EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
Nashville Division

L.W., by and through her parents and next friends, Samantha Williams and Brian Williams, et al.

Plaintiffs,

v.

JONATHAN SKRMETTI, in his official capacity as the Tennessee Attorney General and Reporter, et al.,

Defendants.

Civil No. 3:23-cv-00376

EXPERT DECLARATION OF PAUL W. HRUZ, M.D., PH.D

Pursuant to 28 U.S.C. § 1746, I declare:

1. I have been retained by counsel for Defendants as an expert witness in connection with the above-captioned litigation. I have actual knowledge of the matters stated in this report. My professional background, experience, and publications are detailed in my curriculum vitae. A true and accurate copy of my CV is attached as Exhibit A to this report.

2. I am an Associate Professor of Pediatrics in the Division of Pediatric Endocrinology and Diabetes at Washington University School of Medicine. I also have a secondary appointment as Associate Professor of Cellular Biology and Physiology in the Division of Biology and Biological Sciences at Washington University School of Medicine. I served as Chief of the Division of Pediatric Endocrinology and Diabetes at Washington University from 2012-2017. I served as the Director of the Pediatric Endocrinology Fellowship Program at Washington University from 2008-2016. I am currently serving as Associate Fellowship Program Director at Washington University in St. Louis.

3. Related to the litigation of issues of sex and gender, I have been designated as an expert witness in *Carcaño v. Cooper* (United States District Court for the Middle District of North Carolina, Case No. 1:16-cv-236); *Doe v. Board of Education of the Highland School District* (United States District Court for the Southern District of Ohio, Eastern Division, Case No. 2:16-CV-524); *Whitaker v. Kenosha Unified School District* (United States District Court for the Eastern District of Wisconsin, Case No. 2:16-cv-00943), *Bruce v. South Dakota* (United States District Court for the District of South Dakota, Western Division, Case No. 17-5080); *Kadel v. Falwell* (United States District Court for the Middle District of North Carolina, Case No. 1:19-cv-272-LCB-LPA); *Brandt v. Rutledge* (United States District Court for the Eastern District of Arkansas, Central Division, Case No. 4:21-CV-00450-JM); *D.H. v. Snyder* (United States District Court for

the District of Arizona, Case No. 4:20-cv-00335-SHR), Cause DF-15-09887-SD of the 255th Judicial Circuit of Dallas County, TX regarding the dispute between J.A. D.Y. and J.U. D.Y., Children; *Dekker v. Weida* (United States District Court for the Northern District of Florida, Tallahassee Division, Case No. 4:22-cv-00325-RH-MAF); *Boe v. Marshall* (United States District Court for the Middle District of Alabama Northern Division, Civil Action No. 2:22-cv-184-LCB); and *K.C. v. The Medical Licensing Board of* Indiana (United States District Court for the Southern District Of Indiana Indianapolis Division, No. 1:23-cv-00595-JPH-KMB). I have also served as a science consultant or submitted written testimony for court cases in Canada (B.C. Supreme Court File No. E190334) and Great Britain (*Bell v. Tavistock*).

4. I am being compensated at an hourly rate for actual time devoted, at the rate of $400 per hour including report drafting, travel, testimony, and consultation. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I provide. If called to testify in this matter, I would testify truthfully and based on my expert opinion.

5. My opinions as detailed in this report are based upon my:

a. knowledge, training, and clinical experience in caring for thousands of patients over many years;
b. detailed methodological reviews of hundreds of relevant peer-reviewed science publications;
c. consults, discussions, and team analyses with colleagues and other experts in the field, including attendance and participation in various professional conferences;
d. publications in peer-reviewed scientific journals;
e. editorial work for peer-reviewed scientific journals; and
f. peer-reviewed research grant receipt and review work.

The materials that I have relied upon are the same types of materials that other experts in my field of clinical practice rely upon when forming opinions on the subject, including hundreds of published, peer-reviewed scientific research (and professional) articles.

6. My opinions and hypotheses in this matter are — as all expert reports — subject to the limitations of documentary and related evidence, the impossibility of absolute predictions, and the limitations of social, biological, and medical science. I have not met with, or personally interviewed, anyone in this case. I have not yet reviewed all of the evidence in this case and my opinions are subject to change at any time as new information becomes available to me. Only the trier of fact can determine the credibility of witnesses and how scientific research may or may not be related to the specific facts of any particular case. In my opinion, a key role of an expert witness is to help the court, lawyers, parties, and the public understand and apply reliable scientific, technical, and investigative principles, hypotheses, methods, and information.

BACKGROUND

7. I received my Doctor of Philosophy degree from the Medical College of Wisconsin in 1993. I received my Medical Degree from the Medical College of Wisconsin in 1994.

8. I am board certified in Pediatrics and Pediatric Endocrinology. I have been licensed to practice medicine in Missouri since 2000. My professional memberships include the American Diabetes Association, the Pediatric Endocrine Society, and the Endocrine Society.

9. I have published 62 scholarly articles over my academic career spanning over two decades. This includes peer-reviewed publications in the leading journals in the fields of metabolism, cardiology, HIV, and ethics. Those journals include Gastroenterology, Circulation, Diabetes, Science Signaling, the Journal of Biological Chemistry, and FASEB Journal. See Exhibit A.

10. I have served as a Reviewer for a number of leading science journals in relevant fields including the Journal of Clinical Endocrinology and Metabolism, the Journal of Biological Chemistry, Diabetes, Scientific Reports, and PLOS ONE, assessing the quality of evidence that is put forward for publication. I have also been involved in the evaluation of clinical trials with

colleagues. I have received over $4.6 million in governmental and non-governmental funding for scientific research, including grants from the National Institutes of Health, the American Diabetes Association, The American Heart Association, the March of Dimes, and the Harrington Discovery Institute. I am a member of the Alpha Omega Alpha Medical Honor Society and have received the Armond J. Quick Award for Excellence in Biochemistry, the Eli Lilly Award for Outstanding Contribution to Drug Discovery, and the Julio V. Santiago Distinguished Scholar in Pediatrics Award.

11. During the more than 22 years that I have been in clinical practice, I have participated in the care of hundreds of infants and children, including adolescents, with disorders of sexual development. I was a founding member of the multidisciplinary Disorders of Sexual Development (DSD) program at Washington University. I continue to contribute to the discussion of complex cases and the advancement of research priorities in this field. In the care of these patients, I have acquired expertise in the understanding and management of associated difficulties in gender identification and gender transitioning treatment issues. I have trained and/or supervised hundreds of medical students, residents, and clinical fellows in the practice of medicine.

12. In my role as a scientist and as the Director of the Division of Pediatric Endocrinology at Washington University, I extensively studied the existing scientific research literature related to the incidence, potential etiology, and treatment of gender dysphoria as efforts were made to develop a Transgender Medicine Clinic at Saint Louis Children's Hospital. I have participated in local, national, and international meetings where the endocrine care of children with gender dysphoria has been discussed in detail and debated in depth. I have met individually and consulted with several pediatric endocrinologists (including Dr. Norman Spack) and other professionals spe-

cializing in sexual health (including Eli Coleman) who have developed and led transgender programs in the United States. I have also consulted with, met with, and had detailed discussions with dozens of parents of children with gender dysphoria to understand the unique difficulties experienced by this patient population. I continue to evaluate the ongoing experimental investigation of this condition. I am frequently consulted by other medical professionals to help them understand the complex medical and ethical issues related to this emerging field of medicine.

13. In my clinical practice, I have cared for children from birth to the completion of college in their early twenties who have a variety of hormone-related diseases. This includes disorders of growth, puberty (both precocious and delayed), glucose homeostasis (both hypoglycemia and diabetes mellitus), adrenal function (both adrenal insufficiency and steroid excess), thyroid function, skeletal abnormalities, gonadal dysfunction (including polycystic ovarian syndrome and ovarian failure), hypopituitarism, and disorders of sexual development. Pediatric patients referred to our practice for the evaluation and treatment of gender dysphoria are cared for by an interdisciplinary team of providers that includes a psychologist and pediatric endocrinologist who have been specifically chosen for this role based upon a special interest in this patient population.

BACKGROUND ON SEX AND GENDER

14. Sex is an objective biological trait intrinsically oriented toward specific roles in the conception and development of new members of a species. Both males and females contribute genetic information in distinct yet complementary ways. Males have the role of delivering sperm produced by testes and the unique paternal DNA contained therein to a female. Females have the role of receiving this male genetic information to join with the maternal genetic information contained in ova produced by ovaries. Sex is not "assigned at birth"; it is permanently determined by biology at conception. This remains the standard definition that has been accepted by the relevant

scientific community and used worldwide by scientists, medical personnel, and society in general for decades.[1]

15. The scientific and clinical measurement of sex is done with highly reliable and valid objective methodologies. Visual medical examination of the appearance of the external genitalia is the primary methodology used by clinicians to recognize sex. In cases where genital ambiguity is present, additional testing modalities including chromosomal analysis, measurement of hormone levels, radiographic imaging of internal sexual anatomy and biological response to provocative testing are utilized. The measurement and assessment of biological sex has been documented by valid and reliable research published in credible journals, and is accepted by the relevant scientific community. Medical recognition of an individual as male or female is correctly made at birth in nearly 99.98% of cases according to external phenotypic expression of primary sexual traits (i.e., the presence of a penis for males and presence of labia and vagina for females). [2]

16. For members of the human species (and virtually all mammals), sex is normatively aligned in a binary fashion (i.e., either male or female) in relation to biologic purpose. The presence of individuals with disorders of sexual development (along the range of the established Prader scale) does not alter this fundamental reality.

17. Due to genetic and hormonal variation in the developing fetus, normative development of the external genitalia in any individual differs with respect to size and appearance while maintaining an ability to function with respect to biologic purpose (i.e., reproduction). Internal

[1] See Miller LR, et al. Considering sex as a biological variable in preclinical research. FASEB J. 2017 Jan;31(1):29-34; Clayton JA. Studying both sexes: a guiding principle for biomedicine. FASEB J. 2016 Feb;30(2):519-24.
[2] See L. Sax, How common is Intersex? A response to Anne Fausto-Sterling, 39 J. Sex Rsch. 174 (2002).

structures (e.g., gonad, uterus, vas deferens) normatively align in more than 99.9%+ of mammals with external genitalia, including humans.

18. Due to the complexity of the biological processes that are involved in normal sexual development, it is not surprising that a very small number of individuals are born with defects in this process (1 in 5,000 births).[3] Defects can occur through either inherited or *de novo* mutations in genes that are involved in sexual determination or through environmental insults during critical states of sexual development. Persons who are born with such abnormalities are considered to have a disorder of sexual development (DSD). Most often, this is first detected as ambiguity in the appearance of the external genitalia. Such detection measurements are reliable and valid and accepted by the relevant scientific community.

19. The medical care of persons with DSDs is primarily directed toward identification of the etiology of the defect and treatment of any associated complications. Similar to the diagnosis of other diseases, objective diagnostic tools such as the Prader scale are used to assess, measure, and assign a "stage" to the severity of the deviation from normal. In children with DSDs, characterization based upon phenotype alone does not reliably predict the sex chromosomes present, nor does it necessarily correlate with potential for biological sexual function. The need for making a tentative sex assignment is unique to children with a DSD and does not apply to individuals with normally formed and functional genitalia at birth. Decisions on initial sex assignment in these very rare DSD cases require detailed assessment of objective, reliable medical evidence by a team of expert medical providers. In previous years, the general practice was to make a definitive sex assignment shortly after birth, the belief being that this would allow patients with a disorder of sexual development to best conform to the assigned sex and parents-caregivers to help socialize

[3] *Id*.

the child to the assigned sex. Current practice is to defer sex assignment until the etiology of the disorder is determined and, if possible, a reliable prediction can be made on likely biologic and psychologic outcomes. When this cannot be done with confidence, a presumptive sex assignment is made. Factors used in making such decisions include karyotype (46XX, 46XY, or other), phenotypic appearance of the external genitalia, and parental desires. The availability of new information can, in rare circumstances, lead to a change in sex determination. Decisions on whether to surgically alter the external genitalia to align with sex are generally deferred until the patient is able to provide consent.[4] The tentative assignment of sex is unique to individuals with a DSD.

20. "Gender," a term that had traditionally been reserved for grammatical purposes, is currently used to describe the psychological and cultural characteristics of a person in relation to biological sex. Gender in such new definitions therefore exists only in reference to subjective personal perceptions and feelings and societal expectations, not biology. The reliability and validity of various usages of the term "gender" is currently controversial. The dangers of incorrectly using the term "gender" in place of "sex" have been acknowledged by the Endocrine Society.[5]

21. "Gender identity" refers to a person's individual experience and perception and unverified verbal patient reports of how they experience being male or female or a combination of these or other categories. The term "gender identity" is controversial. There is no current worldwide definition of "gender identity" accepted by the relevant clinical communities. The measurement error rate for "gender identity" is unknown.

[4] See P. A. Lee et al., Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care, 85 Horm. Rsch. Paediatr. 158 (2016).
[5] See A. Bhargava et al., Considering Sex as a Biological Variable in Basic and Clinical Studies: An Endocrine Society Scientific Statement, 42 Endocrine Revs. 219 (2021).

22. People who identify as "transgender" transiently or persistently experience a sex-discordant gender identity.[6]

PUBERTY

23. Puberty is "the morphological and physiological changes that occur in the growing boy or girl as the gonads change from the infantile to the adult state. These changes involve nearly all the organs and structures of the body but they do not begin at the same age nor take the same length of time to reach completion in all individuals. Puberty is not complete until the individual has the physical capacity to conceive and successfully rear children."[7]

24. The principal manifestations of puberty are:

- The adolescent growth spurt; i.e., an acceleration followed by a deceleration of growth in most skeletal dimensions and in many internal organs.
- The development of the gonads.
- The development of the secondary reproductive organs and the secondary sex characters.
- Changes in body composition, i.e., in the quantity and distribution of fat in association with growth of the skeleton and musculature.
- Development of the circulatory and respiratory systems leading, particularly in boys, to an increase in strength and endurance.[8]

25. The ability to physically conceive children is made possible by the maturation of the primary sex characteristics, the organs and structures that are involved directly in reproduction.

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[6] American Psychological Association, The Diagnostic and Statistical Manual of Mental Disorders, (DSM-5), 451 (2013).
[7] W. A. Marshall et al., Puberty, in F. Falkner et al. eds., 2 Human Growth: A Comprehensive Treatise, 2nd ed., (New York: Springer, 1986), 171.
[8] *Id.* at 171-72.

In boys, these organs and structures include the scrotum, testes, and penis while in girls they include the ovaries, uterus, and vagina. In addition to these primary sex characteristics, secondary sex characteristics also develop during puberty — the distinctive physical features of the two sexes that are not directly involved in reproduction. Secondary sex characteristics that develop in girls include "the growth of breasts and the widening of the pelvis," while in boys they include "the appearance of facial hair and the broadening of shoulders." Other patterns of body hair and changes in voice and skin occur during puberty in both girls and boys.[9]

26. Physicians characterize the progress of puberty by marking the onset of different developmental milestones. The earliest visible event, the initial growth of pubic hair, is known as "pubarche;" it occurs between roughly ages 8 and 13 in girls, and between ages 9.5 and 13.5 in boys.[10] In girls, the onset of breast development, known as "thelarche," occurs around the same time as pubarche.[11] "Menarche" is another manifestation of sexual maturation in females, referring to the onset of menstruation, which typically occurs at around 13 years of age and is generally a sign of the ability to conceive.[12] Roughly corresponding to menarche in girls is "spermarche" in boys; this refers to the initial presence of viable sperm in semen, which also typically occurs around 13.[13] (The "-arche" in the terms for these milestones comes from the Greek for beginning or origin). Pubarche and thelarche correspond to the transition from Tanner Stage 1 to Tanner Stage 2 of sexual development. Spermarche and menarche generally occur at Tanner Stage 4 to Tanner Stage 5.

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[9] R. V. Kail et al., Human Development: A Life-Span View 276 (7th ed. 2016).
[10] J. Stang et al., Adolescent Growth and Development 1, 2-3 in J. Stang et al. eds., Guidelines for Adolescent Nutrition Services, (2005), available at http://demoiselle2femme.org/wp-content/uploads/Adolescent-Growth-and-Development.pdf (last visited Apr. 29, 2023).
[11] *Id.* at 2.
[12] Marshall et al., Puberty, at 191-92.
[13] *Id.* at 185.

27. Scientists distinguish three main biological processes involved in puberty: adrenal maturation, gonadal maturation, and somatic growth acceleration. "Adrenarche" — the beginning of adrenal maturation — begins between ages 6 and 9 in girls, and ages 7 and 10 in boys. The hormones produced by the adrenal glands during adrenarche are relatively weak forms of androgens (masculinizing hormones) known as dehydroepiandrosterone and dehydroepiandrosterone sulfate. These hormones are responsible for signs of puberty shared by both sexes: oily skin, acne, body odor, and the growth of axillary (underarm) and pubic hair.[14]

28. "Gonadarche" — the beginning of the process of gonadal maturation — normally occurs in girls between ages 8 and 13 and in boys between ages 9 and 14.[15] The process begins in the brain, where specialized neurons in the hypothalamus secrete gonadotropin-releasing hormone (GnRH).[16] This hormone is secreted in a cyclical or "pulsatile" manner — the hypothalamus releases bursts of GnRH, and when the pituitary gland is exposed to these bursts, it responds by secreting two other hormones.[17] These are luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate the growth of the gonads (ovaries in females and testes in males).[18] (The "follicles" that the latter hormone stimulates are not hair follicles but ovarian follicles, the structures in the ovaries that contain immature egg cells.) In addition to regulating the maturation

[14] S. E. Oberfield et al., Approach to the Girl with Early Onset of Pubic Hair, 96 J. Clin. Endocrinol. & Metabol. 1610 (2011).
[15] S. F. Witchel et al., Puberty: Gonadarche and Adrenarche, in J. F. Strauss III et al. eds., Yen and Jaffe's Reproductive Endocrinology, 6th ed., 395, 395-446.e16 (2009).
[16] A. E. Herbison, Control of Puberty Onset and Fertility by Gonadotropin-Releasing Hormone Neurons, 12 Nature Revs. Endocrinol. 452 (2016).
[17] *Id.* at 453.
[18] *Id.* at 454.

of the gonads and the production of sex hormones, these two hormones also play an important role in regulating aspects of human fertility.[19]

29. As the gonadal cells mature under the influence of LH and FSH, they begin to secrete androgens (masculinizing sex hormones like testosterone) and estrogens (feminizing sex hormones).[20] These hormones contribute to the further development of the primary sex characteristics (the uterus in girls and the penis and scrotum in boys) and to the development of secondary sex characteristics (including breasts and wider hips in girls, and wider shoulders, breaking voices, and increased muscle mass in boys). The ovaries and testes both secrete androgens as well as estrogens, however the testes secrete more androgens and the ovaries more estrogens.[21]

30. The gonads and the adrenal glands are involved in two separate but interrelated pathways (or "axes") of hormone signaling. These are the hypothalamic-pituitary-gonadal (HPG) axis and the hypothalamic-pituitary-adrenal (HPA) axis.[22] Though both play essential roles in puberty, it is, as just noted, the HPG axis that results in the development of the basic reproductive capacity and the external sex characteristics that distinguish the sexes.[23]

31. The third significant process that occurs with puberty, the somatic growth spurt, is mediated by increased production and secretion of human growth hormone, which is influenced by sex hormones secreted by the gonads (both testosterone and estrogen). Similar to the way that

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[19] *Id.* at 452.
[20] M. A. Preece, Prepubertal and Pubertal Endocrinology, in F. Falkner et al. eds., 2 Human Growth: A Comprehensive Treatise, 211, 212 (1986).
[21] R. A. Hess, Estrogen in the adult male reproductive tract: A review, 1 Reproductive Biol. and Endocrinol. 1, (2003); H. G. Burger, Androgen Production in Women, 77 (Suppl.) Fertility and Sterility, S3-5 (2002).
[22] R. D. Romeo, Neuroendocrine and Behavioral Development during Puberty: A Tale of Two Axes, 71 Vitamins and Hormones 1, 1-25 (2005).
[23] M. E. Wierman et al., Neuroendocrine Control of the Onset of Puberty, 2 Human Growth 225 (1986).

the secretion of GnRH by the hypothalamus induces the pituitary gland to secrete FSH and LH, in this case short pulses of a hormone released by the hypothalamus cause the pituitary gland to release human growth hormone.[24] This process is augmented by testosterone and estrogen. Growth hormone acts directly to stimulate growth in certain tissues, and also stimulates the liver to produce a substance called "insulin-like growth factor 1," which has growth-stimulating effects on muscle.[25]

32. The neurological and psychological changes occurring in puberty are less well understood than are the physiological changes. Men and women have distinct neurological features that may account for some of the psychological differences between the sexes, though the extent to which neurological differences account for psychological differences, and the extent to which neurological differences are caused by biological factors like hormones and genes (as opposed to environmental factors like social conditioning), are all matters of debate.

33. Scientists distinguish between two types of effects hormones can have on the brain: organizational effects and activational effects. Organizational effects are the ways in which hormones cause highly stable changes in the basic architecture of different brain regions. Activational effects are the more immediate and temporary effects of hormones on the brain's activity. During puberty, androgens and estrogens primarily have activating effects, but long before then they have organizational effects in the brains of developing infants and fetuses.[26]

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[24] M. A. Preece, Prepubertal and Pubertal Endocrinology, at 218-19.
[25] U. J. Meinhardt et al., Modulation of growth hormone action by sex steroids, 65 Clin. Endocrinol. 413, 414 (2006).
[26] M. M. Herting et al., Puberty and structural brain development in humans, 44 Frontiers in Neuroendocrinol. 122 (2017); J. Hornung et al., Sex hormones and human brain function, 195 Handb. Clin. Neurol. 175 (2020).

34. In sum: Puberty involves a myriad of complex, related, and overlapping physical processes, occurring at various points and lasting for various durations. During this period of life, adrenarche and changes in the secretion of growth hormone contribute to the child's growth and development. With gonadarche, the maturation of sex organs begins and with normal maturation will lead to the emergence of reproductive capacity, as well as the development of the other biological characteristics that distinguish males and females.

PEDIATRIC ENDOCRINE DISORDERS AND TREATMENTS

35. The field of endocrinology is directed toward the care of hormone-related diseases. Pediatric endocrine diseases include disorders of glucose regulation (hypoglycemia and diabetes mellitus), disorders of thyroid function (hyper and hypothyroidism), disorders of growth (e.g., short stature, acromegaly, obesity, and poor weight gain), disorders of sexual development and function (e.g., genital ambiguity, precocious and delayed puberty, hypogonadism, polycystic ovarian syndrome), disorders of adrenal function (e.g., adrenal insufficiency and Cushing's syndrome), disorders of pituitary function, lipid disorders, and disorders of bone and mineral metabolism. For all of these conditions, there are objective physical and biochemical criteria for diagnosis and treatment with well-established normal reference ranges for hormones and metabolites.

I. Using GnRH Analogues — "Puberty Blockers" — to Treat Precocious Puberty and Other Conditions

36. Hormone interventions to suppress puberty were not developed for the purpose of treating children with gender dysphoria. Rather, they were first used as a way to normalize puberty for children who undergo puberty too early, a condition known as "precocious puberty."

37. For females, precocious puberty is defined by the onset of puberty before age 8, while for males it is defined as the onset of puberty before age 9.[27] Premature thelarche (the appearance of breast development) is usually the first clinical sign of precocious puberty in girls. For males, precocious puberty is marked by premature testicular enlargement.[28] In addition to the psychological and social consequences that a child might be expected to suffer, precocious puberty can also lead to reduced adult height, since the early onset of puberty interferes with later bone growth.[29]

38. Precocious puberty is divided into two types, central precocious puberty (sometimes labeled "true precocious puberty") and peripheral precocious puberty (sometimes labeled "precocious pseudopuberty").[30] Central precocious puberty is caused by the early activation of the gonadal hormone pathway by GnRH, and is amenable to treatment by physicians. Peripheral precocious puberty, which is caused by secretion of sex hormones by the gonads or adrenal glands independent of signals from the pituitary gland, is less amenable to treatment. Effects of androgen or estrogen hypersecretion can be reduced by administration of drugs that block the activity of the sex hormone receptors. If a tumor is causing the disorder, surgical removal may be necessary.

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[27] K. O. Klein, Precocious Puberty: Who Has It? Who Should Be Treated?, 84 J. Clin. Endocrinol. & Metabol. 411 (1999). See also F. M. Biro et al., Onset of Breast Development in a Longitudinal Cohort, 132 Pediatrics 1019 (2013); C.-J. Partsch et al., Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens, 7 Human Reproduction Update 292, 293 (2001).
[28] A. Parent et al., The Timing of Normal Puberty and the Age Limits of Sexual Precocity: Variations around the World, Secular Trends, and Changes after Migration, 24 Endocrine Revs. 675 (2011).
[29] J.-C. Carel et al., Precocious puberty and statural growth, 10 Human Reproduction Update 135 (2004).
[30] C.-J. Partsch et al., Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens, at 294-95.

39. Precocious puberty is rare, especially in boys. A recent Spanish study of central precocious puberty estimated the overall prevalence to be 19 in 100,000 (37 in 100,000 girls affected, and 0.46 in 100,000 boys).[31] A Danish study of precocious puberty (not limited to central precocious puberty) found the prevalence to be between 20 to 23 per 10,000 in girls and less than 5 in 10,000 in boys.[32]

40. To diagnose central precocious puberty, hormones from the pituitary gland, LH and FSH, are objectively measured. This can sometimes be done by measurement of baseline levels[33] but often requires assessment after transient stimulation with GnRH. As discussed, these are two hormones that are made in the pituitary gland that signal to the gonads. In males, they lead to production of testosterone. In females, they lead to the production of estrogen. LH and FSH signaling are essential for normal sperm production and ovarian maturation in males and females, respectively.

41. Also subject to objective measurement when diagnosing and treating central precocious puberty are sex steroid hormones, either testosterone or estrogen, and bone growth.

42. Treatment for precocious puberty is somewhat counterintuitive. Rather than stopping the production of GnRH, physicians actually provide patients more constant levels of synthetic GnRH (called GnRH analogues or GnRH agonists).[34] As discussed above, when produced

[31] L. Soriano-Guillén et al., Central Precocious Puberty in Children Living in Spain: Incidence, Prevalence, and Influence of Adoption and Immigration, 95 J. Clin. Endocrinol. & Metabol., 4305, 4307 (2011). In some cases, peripheral precocious puberty is caused by an underlying condition, such as a tumor, that can be treated.
[32] G. Teilmann et al., Prevalence and Incidence of Precocious Pubertal Development in Denmark: An Epidemiologic Study Based on National Registries, 116 Pedriatics 1323 (2005).
[33] S. Heo et al., Basal Serum Luteinizing Hormone Value as the Screening Biomarker in Female Central Precocious Puberty, 24 Annals of Pediatr. Endocrinol. & Metabol., 164, 164-71 (2019).
[34] W. F. Crowley, Jr. et al., Therapeutic use of pituitary desensitization with a long-acting LHRH agonist: a potential new treatment for idiopathic precocious puberty, 52 J. Clin. Endocrinol. &

endogenously (that is, by the body naturally), GnRH stimulates the pituitary gland to release gonad-stimulating hormones (gonadotropins, LH and FSH). When added exogenously, the additional GnRH "desensitizes" the pituitary, leading to a decrease in the secretion of gonadotropins, which in turn leads to the decreased maturation of and secretion of sex hormones by the gonads (ovaries and testes). The intent and effect of giving puberty blockers is identical when it is given to a male as when it is given to a female in this context: suppressing the secretion of gonadotropin hormones. Even the dosing is the same for males and females, and depends on the person's weight.

43. The first publication describing the use of GnRH analogues in children for precocious puberty appeared in 1981.[35] In the time since GnRH analogues were first proposed, they have become fairly well accepted as a treatment of precocious puberty, with one prominent GnRH analogue, Lupron, approved for that use by the FDA in 1993.[36] However, there remain some questions concerning the effectiveness of treatment with GnRH analogues. A 2009 consensus statement of pediatric endocrinologists concluded that GnRH analogues are an effective way to improve the height of girls with onset of puberty at less than 6 years of age, and also recommended the treatment be considered for boys with onset of precocious puberty who have compromised height potential.[37] Regarding the negative psychological and social outcomes associated with precocious puberty, the authors found that the available data were unconvincing, and that additional

Metabol., 370, 370-72 (1981) (LHRH refers to "luteinizing hormone releasing hormone," another term for GnRH.).

[35] *Id.*

[36] "Full Prescribing Information" for Lupron Depot-Ped, FDA.gov (undated), https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020263s036lbl.pdf (last visited April 6, 2023).

[37] J.-C. Carel et al., Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children, 123 Pediatrics e752, e753 (2009).

studies are needed.[38] Puberty blockers have recently been recognized to carry a risk of increased brain pressure that can adversely affect vision and cause severe headaches.[39]

44. When used to treat precocious puberty, the process of desensitization of the pituitary gland by synthetic GnRH is not permanent. After a patient stops taking the GnRH analogues, the pituitary will resume its normal response to the pulsatile secretion of GnRH by the hypothalamus, as evidenced by the fact that children treated for precocious puberty using GnRH analogues will resume normal pubertal development, usually about a year after they withdraw from treatment.[40]

45. The goal of treating precocious puberty is to allow the child to have pubertal development enter the normal quiescence that is present at that age. This treatment helps to preserve their final adult height, by slowing the rate of bone age advancement. The goal is *not* to delay puberty beyond other children, as delaying too long can lead to adverse effects, including reduced bone marrow density, as discussed below.

46. In addition to being prescribed for children with precocious puberty, GnRH analogues have also been used in adults for a variety of indications, including hormone-sensitive tumors.[41] GnRH analogues have also been given to post-pubertal adolescents undergoing chemotherapy with drugs that can have toxic effects on the gonads.[42]

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[38] *Id.*
[39] Risk of pseudotumor cerebri added to labeling for gonadotropin-releasing hormone agonists, AAP News, July 1, 2022, https://publications.aap.org/aapnews/news/20636/Risk-of-pseudotumor-cerebri-added-to-labeling-for?autologincheck=redirected (last visited April 7, 2023).
[40] M. M. Fisher et al., Resumption of Puberty in Girls and Boys Following Removal of the Histrelin Implant, 164 J. Pediatrics 912, 912-16 (2014).
[41] See P. Kumar et al., Gonadotropin-releasing hormone analogs: Understanding advantages and limitations, 7 J. Human Reproductive Scis. 170 (2014).
[42] M. Meli et al., Triptorelin for Fertility Preservation in Adolescents Treated With Chemotherapy for Cancer, 40 J. Pediatr. Hematol./Oncol. 269 (2018).

II. Using Sex Steroids Such as Testosterone and Estrogen to Treat Disorders of Normal Gonadal Function

47. Sex steroids such as testosterone and estrogen are frequently used in the treatment of disorders of normal gonadal function. This includes hypogonadotropic hypogonadism, primary gonadal failure, and delayed puberty.[43] In each of these conditions, there are objective laboratory tests that are used to diagnose these conditions and monitor response to treatment. Deficiency of sex steroids has bodily effects that extend beyond sexual function.[44] This includes significant effect on bone density, lean body mass, metabolism, immunity, and neural function.

48. There are major and highly significant differences between male and female responses to sex hormones.[45] Giving estrogen to a biological male is not equivalent to giving the same hormone to a biological female. Likewise, giving testosterone to a biological female is not equivalent to giving the same hormone to a biological male.[46] Differences are not limited to pharmacokinetic effect (i.e., how drugs are absorbed, distributed throughout the body, and metabolized) but are present even at the cellular level.[47] Sex steroids act by altering the expression of the genetic information present in all nucleated cells of the body. Epigenetic differences (i.e., chemical changes to DNA structure) result in sex-differential expression of over 6,500 genes in the

[43] P. Kumar et al., Male hypogonadism: Symptoms and treatment, 1 J. Advanced Pharmaceutical Technology & Research 297 (2010); K. Voutsadaki et al., Hypogonadism in adolescent girls: treatment and long-term effects, 93 Acta Biomedica Atenei Parmensis e2022317 *1 (2022).
[44] M. Alemany, The Roles of Androgens in Humans: Biology, Metabolic Regulation and Health. 23 Int'l. J. Molecular Scis. 11952 (2022); S. Patel et al., Estrogen: The necessary evil for human health, and ways to tame it, 102 Biomed. & Pharmacother. 403 (2018).
[45] See C. Madla et al., Let's talk about sex: Differences in drug therapy in males and females, 175 Advanced Drug Delivery Revs. 113804 (2021).
[46] See O. P. Soldin et al., Sex Differences in Pharmacokinetics and Pharmacodynamics, 48 Clin. Pharmacokinetics 143 (2009); S. Pogun et al., Sex Differences in Drug Effects, in Encyclopedia of Psychopharmacology, 1210, 1210-16 (I. P. Stolerman, ed., 2010).
[47] See, e.g., C. J. Walker et al., Matters of the heart: Cellular sex differences, 160 J. Molecular and Cellular Cardiol. 42 (2021).

body.[48] Consequences of a failure to recognize these differences can result in drug overdose, lack of treatment response, or serious side effects.

49. Several conditions in male minors may indicate a need for endocrinologic treatment with testosterone. For instance, primary hypogonadism from gonadal failure is caused by damage or impaired function of the male testes. Secondary hypogonadism is caused by abnormalities in pituitary structure or function. Hypogonadism can be objectively diagnosed by measurement of testosterone (or its derivatives) and gonadotropin (LH and FSH) levels. When used for the treatment of affected males with hypogonadism, testosterone is administered to achieve levels that are normal for males of the patient's age. For young adult Tanner Stage 5 males, normal testosterone levels range from 300-900 ng/dL.[49] Achievement of appropriate testosterone levels requires careful monitoring, as excess levels can have serious adverse effects, including elevations of red blood cell counts, changes in blood pressure, and brain changes.[50]

50. Testosterone may also be used in males to treat delayed puberty. To treat the condition of constitutional delay (where the person has means to progress through puberty, but onset was delayed), the male would normally be given low doses of testosterone for 3-4 months to "prime the pump" for normal puberty. Assessment of this condition includes measuring levels of LH, FSH, and testosterone, as well as observation of testicular size. Once puberty has been initi-

[48] M. Gershoni et al., The landscape of sex-differential transcriptome and its consequent selection in human adults, 15 BMC Biol. 7 (2017).
[49] T. G. Travison et al., Harmonized Reference Ranges for Circulating Testosterone Levels in Men of Four Cohort Studies in the United States and Europe, 102 J. Clin. Endocrinol. & Metabol., 1161 (2017).
[50] S. J. Ohlander et al., Erythrocytosis Following Testosterone Therapy, 6 Sexual Medicine Revs. 77 (2018); T. Kienitz et al., Testosterone and Blood Pressure Regulation, 31 Kidney and Blood Press. Rsch. 71 (2008); M. Scarth et al., Androgen abuse and the brain, 28 Curr. Op. in Endocrinol., Diabetes & Obes. 604 (2021).

ated and is progressing, there is no need to administer ongoing testosterone therapy. Normal gonadotropin (LH and FSH) signaling from the pituitary gland will allow continued maturation of the testes, leading to reproductive capacity.

51. Continuing to give external testosterone to a male in normal puberty would suppress the normal function of the testes and can lead to infertility — a result contrary to the goal of endocrinology, which is to restore health. Thus, for instance, a male adolescent undergoing normal puberty who simply desired increased lean body mass (i.e., higher muscle mass) should not normally be given testosterone for that purpose, both because it is considered medically unnecessary and because of the adverse effects of extra testosterone. Among other reasons, these effects explain why testosterone is a controlled substance.

52. Outside the context of gender dysphoria, testosterone is not an indicated treatment for a female child or adolescent. Testosterone, or any androgen, would lead to virilization, which can come with serious adverse effects. This includes impaired fertility, alopecia (hair loss), disfiguring acne, and metabolic changes that increase risk of heart disease and diabetes.[51]

53. Estrogen can be given to young females to treat the same conditions testosterone treats in young males: constitutional delay and hypogonadism, either primary or secondary. Primary hypogonadism is caused by a defect in the presence or function of the ovaries. Secondary hypogonadism is caused by a defect in the structure or function of the pituitary gland. A female can experience premature ovarian insufficiency where the ovaries become inactive over time, both genetically and through environmental incidents. To diagnose these conditions, hormone levels can be objectively measured. This includes LH, FSH, estradiol, and other levels. (Estradiol is a

[51] R. Yang et al., Effects of hyperandrogenism on metabolic abnormalities in patients with polycystic ovary syndrome: a meta-analysis, 14 Reproductive Biol. and Endocrinol. 67 (2016).

form of estrogen, and generally the main hormone followed and measured in female endocrinologic practice.) Female estrogen levels will vary throughout the menstrual cycle but are normally 30-400 pg/mL.[52] The physical response to the intervention can also be measured.

54. Estrogen treatments carry risks, including stroke, elevated blood pressure, and changes to bone development. Males are not generally prescribed estrogen (again, outside the context of gender dysphoria), and there is concern that the risks of estrogen are even higher in males.

GENDER DYSPHORIA AND TREATMENTS

I. Diagnosis

55. In contrast to the conditions discussed above, gender dysphoria is not an endocrine disorder. Instead, it is a diagnostic term for "the distress that may accompany the incongruence between one's experienced or expressed gender and one's" biological sex.[53] Gender dysphoria is associated with high rates of comorbidity, including suicidal ideation, depression, anxiety, poverty, homelessness, eating disorders, and HIV infection.[54] Gender dysphoria as a psychiatric disorder should be distinguished from identifying as transgender or transsexual. As noted, people who identify as transgender "transiently or persistently identify with a gender different from their natal gender." In this definition, "natal gender" refers to sex. Transsexual has an even more specific meaning; it "denotes an individual who seeks, or has undergone, a social transition from male to

[52] S. Verdonk et al., Estradiol reference intervals in women during the menstrual cycle, postmenopausal women and men using an LC-MS/MS method, 495 Clinica Chimica Acta 198, 198-204 (2019).
[53] DSM-5, at 451.
[54] M. D. Connolly et al., The Mental Health of Transgender Youth: Advances in Understanding, 59 J. Adolesc. Health 489 (2016); F. Pinna et al., Mental health in transgender individuals: a systematic review, 34 Int'l Rev. of Psychiatry 292 (2022).

female or female to male, which in many, but not all, cases also involves a somatic transition by cross-sex hormone treatment and genital surgery."[55]

56. The clinical assessment methodology in sex discordant gender medicine is currently limited to self-reported information from patients without objective scientific markers or medical tests. There are no reliable radiological, genetic, physical, hormonal, or biomarker tests that can establish gender identity or reliably predict treatment outcomes.

57. The diagnosis of "gender dysphoria" encompasses a diverse array of conditions. While the contributors to sex-discordant gender identity remain to be fully identified and characterized, differences both in kind and degree within individuals and across varied populations create challenges in establishing specific approaches to alleviate associated suffering. For example, data from adults cannot be assumed to apply equally to children. Nor can data from children who present with sex-discordant gender pre-pubertally be presumed to apply to the growing number of post-pubertal adolescent females presenting with this condition.

58. Although gender perceptions, feelings, and "identity" usually align with biological sex, some individuals report experiencing discordance in these distinct traits. Specifically, for example, biological females may report experiencing that they identify as men and biological males may report experiencing that they identify as women. As gender by definition is distinct from biological sex, one's gender identity does not change a person's biological sex. There is currently no known reliable and valid methodology for assessing the accuracy or nature of unverified, verbal reports of discordant "identity," nor whether that discordant identity will persist or resolve over time. There is thus no known "error rate" for relying upon such reports to engage in hormonal and surgical treatments.

[55] DSM-5, at 451.

II. Treatments

59. Moving from diagnosis to treatment, two broad approaches are generally used to treat children with gender dysphoria.[56]

A. Watchful Waiting and Exploratory Therapy

60. The first approach, sometimes called "watchful waiting," motivated by an understanding of the natural history of transgender identification in children, is to neither encourage nor discourage transgender identification, recognizing that existing evidence (discussed next) shows that the vast majority of affected children are likely to eventually realign their reports of gender identification with their sex. This realignment of expressed gender identity to be concordant with sex is sometimes called "desistance."

61. The "watchful waiting" approach does not advocate doing nothing. Rather, it focuses on affirming the inherent dignity of affected people and supporting them in other aspects of their lives, including the diagnosis and treatment of any comorbidities, as individuals proceed through the various stages of physical and psychological development. For instance, the approach may include the use of scientifically validated treatments (e.g., cognitive behavioral therapy) to treat the patient's anxiety, depression, social skills deficits, or other issues.[57] It may also use exploratory therapy to explore potential causes of the dysphoria, which may be linked to trauma, developmental issues, or psychological comorbidities.

62. Despite differences in country, culture, decade, follow-up length, and method, multiple studies have come to a remarkably similar conclusion: Very few gender dysphoric children

[56] See K. J. Zucker, On the "Natural History" of Gender Identity Disorder in Children, 47 J. Am. Acad. Child & Adolesc. Psychiatry 1361 (2008).
[57] See J. S. van Bentum et al., Cognitive therapy and interpersonal psychotherapy reduce suicidal ideation independent from their effect on depression, 38 Depression and Anxiety 940 (2021).

still want to transition by the time they reach adulthood. Many turn out to have been struggling with sexual orientation issues rather than gender discordant "transgender" identity. The exact number of children who experience realignment of gender identity with biological sex by early adult life varies by study. Estimates within the peer-reviewed published literature range from 50-98%, with most reporting desistance in approximately 85% of children before the widespread adoption of the "affirming" model discussed below.[58] In 2018, for instance, studies found that 67% of children meeting the diagnostic criteria for gender dysphoria no longer had the diagnosis as adults, with an even higher rate (93%) of natural resolution of gender-related distress for the less significantly impacted cases.[59] A March 2021 study, with one of the largest samples in the relevant literature, suggests that most young gender dysphoric children grow out of the condition without medical interventions.[60] Thus, desistance (i.e., the child accepting their natal, biological sex identity and declining "transitioning" treatments) is the outcome for the vast majority of affected children who are not actively encouraged to proceed with sex-discordant gender affirmation.

[58] T. D. Steensma et al., Factors Associated With Desistence and Persistence of Childhood Gender Dysphoria: A Quantitative Follow-Up Study, 52 J. Am. Acad. of Child & Adolesc. Psychiatry 582 (2013); K. D. Drummond et al., A Follow-up Study of Girls with Gender Identity Disorder, 44 Dev. Psychol. 34 (2008); M. S. Wallien et al., Psychosexual Outcome of Gender-Dysphoric Children, 47 J. Am. Acad. Child & Adolesc. Psychiatry 1413 (2008); Bradley SJ, Zucker KJ. Gender Identity Disorder and Psychosexual Problems in Children and Adolescents. The Canadian Journal of Psychiatry. 1990;35(6):477-486

[59] See, e.g., K. J. Zucker, The myth of persistence: Response to "A critical commentary on follow-up studies and 'desistance' theories about transgender and gender non-conforming children" by T. Newhook et al. (2018), 19 Int'l. J. Transgenderism 231 (2018).

[60] See D. Singh et al., A Follow-Up Study of Boys With Gender Identity Disorder, 12 Frontiers in Psychiatry 632784 (2021).

63. Decades of peer-reviewed, published scientific research have supported the efficacy of the psychological approaches for the majority of patients experiencing gender dysphoria.[61] Cognitive therapy and interpersonal psychotherapy have been found to reduce suicidal ideation independent of their effect on depression.[62] Within the "watchful waiting" model, these data support the investigative use of modern psychotherapeutic approaches to address suicidal ideation in children with gender dysphoria (as well as to treat other psychological ailments).

B. Gender Affirming

64. The second, so-called "gender affirming," approach is to affirm the child's present gender identity. This affirmation may have social, medical, legal, and behavioral dimensions. Typically, the "affirming" approach encourages children to embrace transgender identity with social transitioning followed by puberty blockade and hormonal therapy (cross-sex hormones), and potential surgical interventions.[63] This approach is considered below.

65. The first stage of this approach is social affirmation. Included interventions include allowance of name change, use of preferred pronouns, wearing of sex-stereotyped clothing, and access to sex-segregated facilities (bathrooms and locker rooms) corresponding to the child's gender identification. While often presented as a neutral intervention, there is concern that social affirmation will alter the rate of spontaneous desistance. As noted by Steensma et al., "one may

[61] See K. J. Zucker (2008), On the "Natural History," 47 J. Am. Acad. Child & Adolesc. Psychiatry, at 1361, 1361-63; S. J. Bradley et al., Gender Identity Disorder: A Review of the Past 10 Years, 36 J. Am. Acad. Child & Adolesc. Psychiatry 872-80 (1997).
[62] J. S. van Bentum et al. (2021), Cognitive therapy and interpersonal psychotherapy, 38 Depression and Anxiety at 940 (2021); M. W. Gallagher et al., Trajectories of change in well-being during cognitive behavioral therapies for anxiety disorders: Quantifying the impact and covariation with improvements in anxiety, 57 Psychotherapy 379 (2020).
[63] See A. Walch et al., Proper Care of Transgender and Gender Diverse Persons in the Setting of Proposed Discrimination: A Policy Perspective, 106 J. Clin. Endocrinol. & Metabol. 305 (2021).

wonder whether a childhood transition has an effect by itself and influences the cognitive gender identity representation of the child and/or their future development"; this "hypothesized link between social transitioning and the cognitive representation of the self [may] influence the future rates of persistence."[64] For this reason, in the original Dutch protocol social transition of prepubertal children was discouraged. The Dutch protocol authors reference the prior work of Wallien and Cohen-Kettenis[65] in asserting that "because most gender dysphoric children will not remain gender dysphoric through adolescence, we recommend that young children not yet make a complete social transition (different clothing, a different given name, referring to a boy as 'her' instead of 'him') before the very early stages of puberty."[66] In the initial 2009 Endocrine Society guidelines, it was stated that "given the high rate of remission of GID [gender identity disorder] after the onset of puberty, we recommend against a complete social role change and hormone treatment in prepubertal children with GID."[67] Current data validate this concern. In the 2022 study by Olson et al., 94% of children who were socially affirmed persisted with sex-discordant

[64] T. D. Steensma et al., Factors Associated with Desistence and Persistence of Childhood Gender Dysphoria: A Quantitative Follow-up Study, Chapter 6 in T. D. Steensma, From Gender Variance to Gender Dysphoria: Psychosexual development of gender atypical children and adolescents, 97, 115 (Ph.D. thesis, Vrije Universiteit Amsterdam, 2013), available at https://research.vu.nl/ws/files/42117780/hoofdstuk%2006.pdf (last visited May 1, 2023).
[65] M. S. C. Wallien et al. (2008), Psychosexual Outcome of Gender-Dysphoric Children, 47 J. Am. Acad. Child & Adolesc. Psychiatry, at 1413 (2008).
[66] A. L. C. de Vries et al., Clinical management of gender dysphoria in children and adolescents: the Dutch approach, 59 J. Homosex. 301 (2012).
[67] W. C. Hembree et al., Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline, 94 J. Clin. Endocrinol. & Metabol. 3132, 3132-33 (2009).

gender identity.[68] This is in sharp contrast to the low rates of persistence prior to adoption of social affirmation in pre-pubertal children with sex-discordant gender identity.[69]

66. Before analyzing gender affirmative medical interventions, it is important to understand that underlying biology is not changed by altering bodily features to appear as the opposite sex, and such alterations do not change disease vulnerabilities and drug responses associated with genetically defined sex.[70] Despite the increasing ability of hormones and various surgical procedures to reconfigure some male bodies to visually pass as female, or vice versa, the biology of the person remains as defined by genetic makeup, normatively by his (XY) or her (XX) chromosomes, including cellular, anatomic, and physiologic characteristics and the particular disease vulnerabilities associated with that chromosomally-defined sex.[71] For instance, the XX (genetically female) individual who takes testosterone to stimulate certain male secondary sex characteristics will nevertheless remain unable to produce sperm and father children. It is possible for some adolescents

[68] K. R. Olson et al., Gender Identity 5 Years After Social Transition, 150 Pediatrics e2021056082. (2022).
[69] M. S. C. Wallien et al. (2008), Psychosexual Outcome of Gender-Dysphoric Children, 47 J. Am. Acad. Child & Adolesc. Psychiatry, at 1413-23. The rate of persistence in this study was 27%. *Id.* at 1413, 1416, 1420.
[70] See Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016 Oct;16(10):626-38 and Karlsson Lind L, et al. Sex differences in drugs: the development of a comprehensive knowledge base to improve gender awareness prescribing. Biol Sex Differ. 2017 Oct 24;8(1):32.
[71] See Exploring the biological contributions to human health: does sex matter?, (Institute of Medicine (U.S.), T. M. Wizemann, & M. L. Pardue eds., 2001) (hardcover edition); Exploring the Biological Contributions to Human Health: Does Sex Matter?, (2001), http://www.nap.edu/catalog/10028 (last visited Apr 8, 2023) (electronic editions).

and adults to pass unnoticed as the opposite gender that they aspire to be — but with limitations, costs, and risks.[72] And their underlying biology does not change.

1. Puberty Blockers

67. Only in the 1990s did GnRH analogues begin being used to suppress puberty in children who identify as the opposite sex. In 1998, Peggy Cohen-Kettenis and Stephanie van Goozen, psychologists at a Dutch gender clinic, described the case of a 13-year-old female gender-dysphoria patient, on whom a GnRH analogue was used to suppress puberty before the patient received a definitive diagnosis of gender identity disorder at age 16. At age 18, the patient underwent sex-reassignment surgery.[73]

68. The clinic's scientists developed an influential protocol, often referred to as the "Dutch protocol," which involved puberty suppression followed by cross-sex hormones and potential surgical interventions.[74] In many clinics that adhere to the gender affirmation model, the ages for initiating sex-discordant, gender-affirming, sex-steroid hormones has deviated substantially from the original Dutch protocol. In current protocols puberty blockers (GnRH analogs) are initiated as soon as puberty begins (Tanner Stage 2), which can occur as early as 8 years in females and 9 years in males. While in the Dutch protocol, cross-sex hormones started at 16 years, the Standards of Care for the Health of Transgender and Gender Diverse People, Version

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[72] See S. B. Levine, Informed Consent for Transgendered Patients, 45 J. Sex & Marital Therapy, 218 at *6 (2018) ("Informed Consent"); S. B. Levine, Reflections on the Legal Battles Over Prisoners with Gender Dysphoria, 44 J. Am. Acad. Psychiatry & L. 236, 238 (2016) ("Reflections on Legal Battles").

[73] P. T. Cohen-Kettenis et al., Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent, 7 Eur. Child & Adolesc. Psychiatry 246 (1998). See also P, T. Cohen-Kettenis et al., Treatment of Adolescents With Gender Dysphoria in the Netherlands, 20 Child and Adolesc. Psychiatric Clinics of N. Am. 689 (2011).

[74] M. Biggs, The Dutch Protocol for Juvenile Transsexuals: Origins and Evidence, J. Sex & Marital Therapy, 1 (Sept.19, 2022).

8 (SOC-8), the latest guidelines published by the World Professional Association for Transgender Health (WPATH), made no recommendations on specific ages for initiation of gender-affirming medical interventions, stating that decisions need to be made on an individual basis with the possibility of there being compelling reasons to start interventions earlier.[75] Gender-affirming surgery in the Dutch model was reserved to patients 18 years or older. Again, WPATH discusses surgery for minors, noting that "[c]hest masculinization surgery can be considered in minors when clinically and developmentally appropriate," and suggesting that "there may be a benefit for some adolescents to having [vaginoplasties] performed before the age of 18."[76] GnRH analogs are discontinued after gonadectomy is performed as this medication is no longer needed to suppress gonads that are no longer present. Due to the suppressive effect of exogenous sex-steroids on gonadal function, GnRH analogs are often stopped after gender-affirming hormone administration has been titrated to maximal doses required to achieve the desired change in secondary sex characteristics.

69. This gender "affirming" model, with its reliance on hormones and surgical interventions, would make gender dysphoria unique among psychiatric conditions: sex reassignment surgery "for Gender Dysphoria is symptom based. It does not correct a biological abnormality.[77] The same is true for hormone-based interventions.

[75] E. Coleman et al., Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, 23 Int'l. J. Transgender Health, 51-5258, 556-66, S1, S65-66 (Sept. 6, 2022) ("SOC-8").
[76] *Id.* at 566.
[77] S. B. Levine (2016), Reflections on Legal Battles, 44 J. Am. Acad. Psychiatry & L., at 240.

70. These scientists, along with others, have claimed that puberty suppression is "fully reversible."[78] On this view, puberty suppression "give[s] adolescents, together with the attending health professional, more time to explore their gender identity, without the distress of the developing secondary sex characteristics. The precision of the diagnosis, it is claimed, may thus be improved."[79]

71. This assertion appears to presume that natural sex characteristics interfere with the "exploration" of gender identity, when one would expect that the development of natural sex characteristics might contribute to the natural consolidation of one's gender identity. It is based upon an untested scientific premise that interfering with the development of natural sex characteristics can allow for a more accurate diagnosis of the gender identity of the child. Given that nearly all gender dysphoric adolescents who begin puberty blockers proceed to cross-sex hormones,[80] it seems more plausible that the interference with normal pubertal development will influence the gender identity of the child by reducing the prospects for developing a gender identity corresponding to his or her biological sex.

72. Given their potential importance in the lives of the affected children, claims about reversibility require careful examination. In developmental biology, it makes little sense to describe anything as "reversible." If a child does not develop certain characteristics at age 12 because

[78] H. A. Delemarre-van de Waal et al., Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects, 155 Eur. J. of Endocrinol., S131, S133 (Nov. 1, 2006).
[79] P. T. Cohen-Kettenis et al., The Treatment of Adolescent Transsexuals: Changing Insights, 5 J. Sexual Med. 1892, 1894 (2008).
[80] M. A. T. C. van der Loos et al., Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands, 6 Lancet Child & Adolesc. Health 869 (2022).

of a medical intervention, then his or her developing those characteristics at age 18 is not a "reversal," since the sequence of development has already been disrupted. This is especially important since there is a complex relationship between physiological and psychosocial development during adolescence. Gender identity is shaped during puberty and adolescence as young people's bodies become more sexually differentiated and mature. Given how little we understand about gender identity and how it is formed and consolidated, we should be cautious about interfering with the normal process of sexual maturation.

73. A more relevant question is whether the physiological and psychosocial development that occurs during puberty can resume in something resembling a normal way after puberty-suppressing treatments are withdrawn. In children with precocious puberty, this does appear to be the case. Puberty-suppressing hormones are typically withdrawn around the average age for the normal onset of gonadarche, at about age 12, and normal hormone levels and pubertal development gradually resume. For one common method of treating precocious puberty, girls reached menarche approximately a year after their hormone treatments ended, at an average age of approximately 13, essentially the same average age as the general population.[81] The evidence for the safety and efficacy of puberty suppression in boys is less robust, chiefly since precocious puberty is much rarer in boys. Although the risks are speculative and based on limited evidence, boys who undergo puberty suppression may be at greater risk for the development of testicular microcalcifications, which may be associated with an increased risk of testicular cancer, and puberty suppression in boys may also be associated with obesity.[82]

[81] M. M. Fisher et al., Resumption of Puberty in Girls and Boys Following Removal of the Histrelin Implant, 164 J. Pediatrics 912, 912-16 (2014).
[82] S. Bertelloni, Treatment of central precocious puberty by GnRH analogs: long-term outcome in men, 10 Asian J. Androl. 525, 531 (2008).

74. Unlike children affected by precocious puberty, adolescents with gender dysphoria do not have any physiological disorders of puberty that are being corrected by the puberty-suppressing drugs. The fact that children with suppressed precocious puberty between ages 8 and 12 resume puberty at age 13 does not mean that adolescents suffering from gender dysphoria whose puberty is suppressed beginning at age 12 will simply resume normal pubertal development later if they choose to withdraw from the puberty-suppressing treatment and choose not to undergo other sex-reassignment procedures. Interrupting puberty in this manner may have significant effects on final stature and bone density.[83]

75. After an extended period of pubertal suppression one cannot "turn back the clock" and reverse changes in the normal coordinated pattern of adolescent psychological development and puberty.[84] Once puberty is blocked, even if eventually unblocked (and assuming signaling from the pituitary gland resumes), the person cannot "buy back" the time when the physical process of puberty has been disrupted at the time when it would normally occur with complementary psychological processes in that stage in the person's life.

76. A possible effect of blocking normally timed puberty is alteration of normal adolescent brain maturation.[85]

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[83] T. Joseph et al., The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort, 32 J. Pediatric Endocrinol. and Metabol. 1077, 1077-81 (2019); D, Klink et al., Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria, 100 J. Clin. Endocrinol. & Metabol., E270-E275 (2015).

[84] See P. W. Hruz et al., Growing Pains, 52 The New Atlantis: A Journal of Technology and Society, 3 (Spring 2017). See also N. Vijayakumar et al., Puberty and the human brain: Insights into adolescent development, 92 Neurosci. & Biobehav. Revs 417 (2018); S. Choudhury, Culturing the adolescent brain: what can neuroscience learn from anthropology?, 5 Social Cognitive and Affective Neurosci. 159 (2010).

[85] See M. Arain et al., Maturation of the adolescent brain, 9 Neuropsychiatric Disease and Treatment, 449 (2013).

77. Another troubling question that has been largely uninvestigated is what psychological consequences there might be for children with gender dysphoria whose puberty has been suppressed and who later come to identify as their biological sex.

78. In addition to the reasons to suspect that puberty suppression may have side effects on physiological, psychological, and brain development, the evidence that something like normal puberty will resume for these patients after puberty-suppressing drugs are removed is very weak. Data obtained from the treatment of precocious puberty cannot be assumed to apply equally to the disruption of puberty that begins after 8 years of age in females and after 9 years of age in males.

79. In addressing the concern of puberty blockers on bone density, it is important to recognize that bone density is normally increasing during the teenage years. Observing an increase in bone density measurement does not indicate lack of adverse effect.[86] The relevant parameter is the bone density in relation to mean bone density in age and size matched controls. This is generally assessed as a "z-score." In the study by Klink,[87] it was observed that with blockade of normally timed puberty, there was a failure to regain pre-treatment z-scores for bone density even after introduction of cross-sex hormones. This supports the concern that interruption of normally timed puberty adversely affects bone density.

2. Cross-Sex Hormones

80. Rather than resuming biologically normal puberty, adolescents treated on the "affirming" model overwhelmingly go from suppressed puberty to medically conditioned cross-sex

[86] L. K. Bachrach, Acquisition of optimal bone mass in childhood and adolescence, 12 Trends in Endocrinol. & Metabol. 22 (2001).
[87] Klink et al., Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria, 100 J. Clin. Endocrinol. & Metabol., E270-E275 (2015)

puberty, when they are administered cross-sex hormones.[88] Specifically, exogenous estrogen is administered to biological men to induce gynecomastia (i.e., the enlargement of breast tissues), and testosterone is administered to biological women to induce virilization (i.e., the development of facial hair and other desired male features) and to interfere with normal ovarian function.

81. Along with (and often before) estrogen is administered to biological males in this treatment, spironolactone may be used as an androgen blocker. Spironolactone is primarily used for the treatment of blood pressure and heart failure. It is a mineralocorticoid antagonist, meaning that it blocks the function of proteins in the kidney that regulate salt retention. But it also has effects in blocking the action of androgens. As discussed, androgens are masculinizing hormones that lead to virilization. Testosterone is a prime androgen, but other androgens are also made in the gonads and adrenal gland. Spironolactone is sometimes used in the treatment of polycystic ovarian syndrome, in which females will undergo virilization due to excess androgen production in the ovaries. This syndrome can have adverse effects on fertility, metabolic health, and cardio-vascular health.[89] The diagnosis of polycystic ovarian syndrome is a clinical diagnosis based upon the physical evidence of virilization or androgen effects, insulin resistance, and irregular periods. There are objective biological measures to assess those androgen levels, most notably elevated free testosterone levels. And there are objective measures of dysregulation of relevant signals from the pituitary gland, the LH and the FSH, to complement the clinical diagnosis by looking at the degree of virilization that is present in the patient.

[88] M. A. T. C. van der Loos et al. (2022), Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence, 6 Lancet Child & Adolesc. Health, at 869-75.
[89] M. H. Hunter et al., Polycystic Ovary Syndrome: It's Not Just Infertility, 62 Am. Fam. Physician 1079, 1079-88 (2000).

82. Spironolactone would not be prescribed to male patients for an endocrinologic purpose related to androgen production. Once again, this reflects a fundamental biological difference between males and females. Though spironolactone can be used to regulate the levels of potassium and sodium in the body, such treatment would be based on objective markers of those levels.

83. Likewise, the administration of the sex steroid hormones differ by the sex of the individual. It is not identical to give testosterone to a male as it is to give it to a female, nor is it the same treatment to give estrogen to a male versus female. This difference has an established scientific basis. The differences between males and females occurs in every nucleated cell of the body, for males and females have different genetic programming. This is a process known as epigenetics, meaning that there are modifications of the DNA itself that alter the expression of genes when exposed to the same stimulus. As noted above, there are over 6,000 sex-differentially expressed genes. So, if one gives testosterone to a male, the physiologic effects of that treatment, even in the measurement at which genes are turned on and turned off, will be different than if one gives testosterone to a female.[90]

84. In congenital or acquired conditions where there is a defect in the ability to produce endogenous sex-steroid hormones, the goal of administering testosterone or estrogen is to restore the body to its natural state had the defect not been present. For example, females with Turner syndrome have premature ovarian failure and are therefore given estrogen to preserve bone health and allow normal pubertal maturation. Males with Klinefelter syndrome have primary hypogonad-

[90] M. Gershoni et al., The landscape of sex-differential transcriptome and its consequent selection in human adults, 15 BMC Biol. 7 (2017)

ism and are therefore given testosterone to achieve normal lean body mass, bone density, hematocrit, and other androgen mediated bodily changes. Importantly, sex-steroid hormone doses are adjusted to maintain levels within the normal range for the sex of that individual.

85. While the normal range for testosterone levels in a male adolescent who has completed puberty is 300-900 ng/dL, testosterone levels for a female adolescent are 15-70 ng/dL. Testosterone levels can be elevated in females with pathologic conditions such as polycystic ovarian syndrome, but levels generally are less than 150 ng/dL. Levels above 200 ng/dL would generally necessitate evaluation for an adrenal or ovarian tumor.

86. When a patient with gender dysphoria is placed on cross-sex hormones, per the Dutch protocol, puberty-suppressing GnRH analogues continue to be administered until exogenous administration of cross-sex hormones (i.e., sex hormones normally produced by the gonads of the opposite sex) leads to sufficient suppression of endogenous sex hormone production, or the gonads are surgically removed. With pubertal blockade, sex hormones that are normally secreted by the maturing gonads are not produced. This means that adolescents undergoing cross-sex hormone treatment circumvent the most fundamental form of sexual maturation — the maturation of their reproductive organs.

87. For males who are being medically transitioned, exogenously administered estrogen will suppress testosterone production through feedback inhibition of pituitary LH and FSH secretion. Without pubertal blockade, this reduction of endogenous testosterone production is usually not sufficient to fully prevent virilization, and it is therefore necessary to add anti-androgenic medications such as spironolactone. For females being medically transitioned, exogenously administered testosterone will usually result in the cessation of menses and lead to the expected effect of virilization.

88. Patients undergoing gender affirming surgery discontinue GnRH treatment after having their gonads removed, since the secretion of sex hormones that the treatment is ultimately intended to prevent will no longer be possible. These patients are then sterile, as loss or alteration of primary sexual organs leads directly to impairment of reproductive potential.

89. Although the long-term effect of exposing immature gonads to cross-sex hormones is currently unknown, it is generally accepted, even by advocates of transgender hormone therapy, that hormonal treatment impairs fertility, which may be irreversible.[91] Specifically, estrogen administration to males who identify as women results in impaired spermatogenesis and an absence of Leydig cells in the testis.[92] Exogenous testosterone administration to females who identify as men causes ovarian stromal hyperplasia and follicular atresia.[93] Recognition of these consequences is the basis for the development of new areas of medical practice where there is an attempt to restore fertility that has been intentionally destroyed.[94]

90. Gametes (sperm and ova) require natural puberty to mature to the point that they are viable for reproduction.[95] While it is expected that the exposure of immature gonads to cross-sex hormones will lead to infertility, whether affected individuals have permanent sterility has not

[91] See L. Nahata et al., Low Fertility Preservation Utilization Among Transgender Youth, 61 J. Adolesc. Health 40 (2017).
[92] C. Schulze, Response of the human testis to long-term estrogen treatment: Morphology of Sertoli cells, Leydig cells and spermatogonial stem cells, 251 Cell and Tissue Rsch. 31 (1988).
[93] T. D. Pache et al., Ovarian morphology in long-term androgen-treated female to male transsexuals. A human model for the study of polycystic ovarian syndrome?, 19 Histopathol. 445 (1991); K. Ikeda et al., Excessive androgen exposure in female-to-male transsexual persons of reproductive age induces hyperplasia of the ovarian cortex and stroma but not polycystic ovary morphology 28 Human Reproduction 453 (2013).
[94] See, e.g., A. J. Ainsworth et al., Fertility Preservation for Transgender Individuals: A Review, 95 Mayo Clinic Proceedings 784, 784-92 (2020).
[95] H. E. Kuhn et al., The Onset of Sperm Production in Pubertal Boys: Relationship to Gonadotropin Excretion, 143 Am. J. Diseases in Children 190 (1989).

been established. Much of the uncertainty arises from the novelty of this intervention and the lack of long term follow up. There are limited reports of successful pregnancies after cross-sex hormones, but all of the subjects started gender-affirming hormones as adults after completing puberty.[96] I am not aware of any reports that show this for children who were exposed to puberty blockers before completing puberty followed by cross-sex hormones.

91. There are many other known risks to puberty suppression followed by cross-sex hormones beyond fertility concerns. As noted, emerging data show that treated patients have lower bone density, which may lead to increased fracture risk later in life.[97] Other potential adverse effects include disfiguring acne, high blood pressure, weight gain, abnormal glucose tolerance, breast cancer, liver disease, thrombosis, and cardiovascular disease.[98] In addition, non-physiological levels of estrogen in males has been shown to increase the risk of thromboembolic stroke above the incidence observed in females.[99]

92. Advocates of the gender affirmation approach to gender dysphoria often make misleading or erroneous statements about the potential or known adverse effects of interrupting normally timed puberty with GnRH analogues and the administration of "gender-affirming" sex-

[96] I. de Nie et al., Successful restoration of spermatogenesis following gender-affirming hormone therapy in transgender women, 4 Cell Reports Med. 100858 (2023).
[97] See D. Klink et al. (2015), Bone Mass in Young Adulthood, 100 J. Clin. Endocrinol. & Metabol., at E270-E275.
[98] See L. J. Seal, A review of the physical and metabolic effects of cross-sex hormonal therapy in the treatment of gender dysphoria, 53 Annals Clin. Biochem. 10 (2016); K. Banks et al., Blood Pressure Effects of Gender-Affirming Hormone Therapy in Transgender and Gender-Diverse Adults, 77 Hypertension 2066, 2066-74 (2021); D. Getahun et al., Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study, 169 Annals of Internal Med. 205 (2018); S. Maraka et al., Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis, 102 J. Clin. Endocrinol. & Metabol., 3914, 3914-23 (2017).
[99] See, e.g. D. Getahun et al. (2018), Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons, 169 Annals of Internal Med., at 205, *6-*8.

steroid hormones. This includes appeal to data on the safety of using these drugs in treating precocious puberty, where the effect of the intervention is to restore the patient to the normal phase of quiescence of the pituitary-gonadal axis. Further assertions that such treatments are the same as those used to treat conditions that are associated with infertility, such as Turner syndrome and Klinefelter syndrome, ignore the striking differences in both physiological attributes and goal of intervention. Some potential adverse effects can only be ascertained with directed testing that goes beyond what is normally performed as screening tests done in medical clinics. Cancer and cardiovascular and metabolic risks often take decades to manifest. The failure to observe patients with myocardial infarction (heart attack), thromboembolic events (stroke), or cancer in adolescent patients exposed to testosterone or estrogen at levels at or exceeding those observed in known disease states (e.g., polycystic ovarian syndrome or hormone-secreting tumors) does not mitigate concerns with these interventions in youth who experience sex-discordant gender identity.

ENDOCRINE SOCIETY AND WPATH GUIDELINES

93. A reasonable understanding of relative risk versus benefit for medical products or procedures is a fundamental obligation in providing appropriate clinical care. This is the bedrock standard of "evidence-based medical practice." When considering clinical practice guidelines, it is essential that physicians recognize the relative risks and benefits of such documents. If done properly, they can distill large data sets into actionable clinical recommendations. However, there is a long history of clinical practice guidelines that have later been found to be deficient, resulting in wasted medical resources, failure to achieve desired benefits, and, at times, substantial harm to patients.[100]

[100] See S. H. Woolf et al., Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines, 318 BMJ 527 (1999).

94. As detailed throughout this report, this foundational standard of "evidence-based medical practice" has never been met as to so-called gender affirming care. The field of "affirming care" is characterized by a poor quality of evidence regarding safety and efficacy, as well as attempts to silence standard scientific discussion and consideration of alternative hypotheses; failures to acknowledge existing data showing persistence of suicidality after intervening; the intentional impairment and destruction of normally formed and functioning male and female sexual organs to address psychological-psychiatric distress; the manipulation of language from standard medical definitions; and widespread failures to properly report research data related to gender transitioning.

95. Despite the dangers of confirmation bias, existing guidelines base recommendations for "affirming" medical interventions on uncorroborated patient self-reports, assessed by mental health professionals with no methodology for discerning accurate patient reports, no alternative treatments offered, and no alternative explanations (e.g., social contagion) explored. There is no biological test to verify the diagnosis.

I. Endocrine Society

96. In 2009, the Endocrine Society published clinical guidelines for the treatment of patients with persistent gender dysphoria.[101] The recommendations include temporary suppression of pubertal development of children with GnRH agonists followed by hormonal treatments to induce the development of secondary sexual traits consistent with one's gender identity. In developing these guidelines, the authors assessed the quality of evidence supporting the recommendations made with use of the GRADE (Grading of Recommendations, Assessment, Development,

[101] See W. C. Hembree et al. (2009), Endocrine Treatment of Transsexual Persons, 94 J. Clin. Endocrinol. & Metabol. at 3132, 3132-54.

and Evaluation) system for rating clinical guidelines. As stated in the Endocrine Society publication, "the strength of recommendations and the quality of evidence was low or very low."[102] According to the GRADE system, low recommendations indicate that "[f]urther research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate."[103] Very low recommendations mean that "any estimate of effect is very uncertain."[104]

97. The Endocrine Society published an updated set of guidelines in September 2017.[105] Those guidelines show that all recommendations as to "affirming" treatment of adolescents are supported by low or very low-quality evidence.[106] Despite this low-quality evidence in this document, strong recommendations are frequently made on the basis of the "values and preferences" of either the Endocrine Society or the patient.[107] For instance, the Endocrine Society's recommendations expressly place "a lower value on avoiding potential harm from early pubertal suppression."[108]

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[102] *Id.* at 3132.
[103] G. H. Guyatt et al., GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, 336 BMJ 924, 926 (2008).
[104] *Id.*
[105] See W. C. Hembree et al., Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline, 102 J. Clin. Endocrinol. & Metabol., 3869, 3869-3903 (2017). See also Corrigendum for "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," 103 J. Clin. Endocrinol. & Metabol. 2758 (July 2018) ("Endocrine Society Clinical Practice Guideline"); Corrigendum for "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," 103 J. Clin. Endocrinol. & Metabol. 699 (Feb. 2018).
[106] J. Block, Gender dysphoria in young people is rising — and so is professional disagreement, 380 BMJ 382, at *2 (2023). See also W. C. Hembree et al. (2017), Endocrine Society Clinical Practice Guideline, 102 J. Clin. Endocrinol. & Metab. at 3869-3903.
[107] See, e.g., W. C. Hembree et al. (2017), Endocrine Society Clinical Practice Guideline, 102 J. Clin. Endocrinol. & Metab., at 3872-73, 3881, 3894.
[108] *Id.* at 3881.

98. Dr. Guyatt, a co-developer of the GRADE system, "found 'serious problems' with the Endocrine Society guidelines, noting that the systematic reviews didn't look at the effect of the interventions on gender dysphoria itself, arguably 'the most important outcome.'"[109] He also criticized the Endocrine Society guidelines for pairing strong recommendations with weak evidence, explaining that such practice is discouraged "except under very specific circumstances."[110] He states that except under very specific circumstances, such practice is discouraged.[111]

99. The Endocrine Society guidelines state that "[w]eak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action."[112] These values and preferences include the desire of the individual seeking gender-affirming medical interventions, who may be operating under an *a priori* presumption (encouraged by the Endocrine Society's "strong recommendations") that these will lead to improved mental health. As detailed throughout this declaration, the existing data do not support this presumption. Instead, the existing data substantiate Dr. Guyatt's concerns as summarized by J. Block:

> For Guyatt, claims of certainty represent both the success and failure of the evidence-based medicine movement. "Everybody now has to claim to be evidence based" in order to be taken seriously, he says—that's the success. But people "don't particularly adhere to the standard of what is evidence based medicine—that's the failure." When there's been a rigorous systematic review of the evidence and the bottom line is that "we don't know,'" he says, then "anybody who then claims they do know is not being evidence based."[113]

[109] J. Block (2023), Gender dysphoria in young people is rising, 380 BMJ 382, at *2-*3.
[110] *Id.* at *3.
[111] *Id.*
[112] W. C. Hembree et al. (2017), Endocrine Society Clinical Practice Guideline, 102 J. Clin. Endocrinol. & Metab., at 3872-73, 3885.
[113] J. Block (2023), Gender dysphoria in young people is rising, 380 BMJ 382, at *4.

100. It is highly misleading to imply that the current Endocrine Society guidelines[114] represent the opinions of the Society's 18,000 members. The committee that drafted these guidelines was composed of *less than a dozen* members. The guidelines were never submitted to the entire Endocrine Society membership for comment and approval prior to publication. They also did not undergo external review. Such methodologies are common in association "statements" and "endorsement;" they are not scientific or generally reliable.

101. The panel that drafted the Endocrine Society guidelines was heavily composed of individuals who have significant associations with WPATH. Specifically, all but one of the committee members were leaders in WPATH. Two of the authors served as WPATH's president (Walter J. Meyer and Vin Tangpricha);[115] at least five have served, or are serving, on WPATH's Board of Directors (Peggy Cohen-Kettenis, Louis Gooren, Stephen Rosenthal, Joshua Safer, Guy T'Sjoen);[116] and at least four (Stephen Rosenthal, Joshua Safer, Vin Tangpricha, and Guy T'Sjoen)

[114] W. C. Hembree et al. (2017), Endocrine Society Clinical Practice Guideline, 102 J. Clin. Endocrinol. & Metab., at 3872.

[115] A. Devor, History, WPATH World Professional Association for Transgender Health, https://www.wpath.org/about/history (last visited Apr 12, 2023) (Walter Meyer III, M.D. (President, 2003-2005)); Profile, Vin Tangpricha MD/PHD, Emory School of Medicine, https://med.emory.edu/departments/medicine/divisions/endocrinology/profile/?u=VTANGPR (last visited Apr 12, 2023).

[116] A. Devor, History, WPATH (Peggy Cohen-Kettenis (Board of Directors, 2003-2005), Louis J. G. Gooren, MD (Board of Directors, 1999-2003)); WPATH, Executive Committee and Board of Director, WPATH World Professional Association for Transgender Health, https://www.wpath.org/about/EC-BOD (last visited Apr 12, 2023) (Stephen Rosenthal, MD (Board of Directors, Member-at-Large, 2020-2024), Joshua Safer, MD (Board of Directors, Member-at-Large, 2022-2026), Guy G. R. T'Sjoen, MD, PhD (EPATH Representative — Term Determined by Board of Directors)).

were authors of WPATH SOC-8[117]. Three (Peggy Cohen-Kettenis, Walter Meyer, and Vin Tangpricha) were authors of WPATH SOC-7.[118]

II. WPATH

102. The World Professional Association for Transgender Health (WPATH) has also issued several iterations of guidelines. The first set of clinical practice guidelines was published in 1979. WPATH published its latest version of their "Standards of Care for the Health of Transgender and Gender Diverse People" (SOC-8) in September 2022.[119] While this document has been presented as "authoritative" and "evidence-based," numerous concerns have been raised about the updated recommendations. Changes in SOC-8 include removal of age limits for initiation of cross-sex hormones and gender-affirming surgery,[120] recommendations with language sufficiently flexible to encourage the exclusion of parents from the decision-making process if they

[117] E. Coleman et al. (2022), SOC-8, 23 Int'l. J. Transgender Health, at 51-5258.
[118] E. Coleman et al., Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7, 13 Int'l. J. Transgenderism 165 (2012) ("SOC-7").
[119] E. Coleman et al. (2022), SOC-8, 23 Int'l. J. Transgender Health, at 51-5258, S1-259.
[120] See, e.g., J. Block (2023), Gender dysphoria in young people is rising, 380 BMJ 382, at *1.

question or challenge medical interventions,[121] elimination of safeguards for addressing underlying mental health illness before the start of gender-affirming medical interventions,[122] and the addition of a section on "eunuch-identified" people.[123] Many of the recommendations made reflect WPATH's acknowledged agenda as an advocacy group. In SOC-8, WPATH specifically states, "Health is promoted through public policies and legal reforms that advance tolerance and equity for gender diversity and that eliminate prejudice, discrimination, and stigma. WPATH is committed to advocacy for these policy and legal changes."[124] Despite the claim that the SOC-8 guidelines are based upon solid scientific evidence, such recommendations represent ideological positions devoid of rigorous scientific evidence.[125] Scientific data on long-term outcomes in adolescents who are exposed to the U.S. affirmation model simply do not exist.

103. In sum, clinical guidelines or standards of care should provide practitioners with evidence-based standards by which they may reliably inform the patient of projected outcomes, and do so with a known error rate. Such data is the starting point for obtaining informed consent. This information is not provided by either WPATH or Endocrine Society's guidelines.

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[121] See, e.g., E. Coleman et al. (2022), SOC-8, 23 Int'l. J. Transgender Health, at 5548 and Recommendation 6.11 ("We recommend when gender-affirming medical or surgical treatments are indicated for adolescents, health care professionals working with transgender and gender diverse adolescents involve parent(s)/guardian(s) in the assessment and treatment process, unless their involvement is determined to be harmful to the adolescent *or not feasible*." (emphasis added)).

[122] P. Toro, 7 takeaways for HR from the new transgender guidelines, HR Executive (2022), https://hrexecutive.com/7-takeaways-for-hr-from-the-new-transgender-guidelines/ (last visited Apr 29, 2023) ("Operationally, this means that TGD individuals do not require a mental health evaluation in order to obtain medical or surgical services. This is quite different from the prior guideline, which required mental health sign-off from one or two mental health providers in order to obtain gender-affirming surgery.").

[123] E. Coleman et al. (2022), SOC-8, 23 Int'l. J. Transgender Health, at 51-5258, S1-259.

[124] *Id.* at 55.

[125] See, e.g., J. Block (2023), Gender dysphoria in young people is rising, 380 BMJ 382, at *1-*3.

INFORMED CONSENT

104. The fundamental purpose of the practice of medicine is to treat disease and alleviate suffering. An essential tenet of medical practice is to avoid doing harm in the process. As discussed above, relying on clear, valid, reliable, and definitive evidence on how to best accomplish treatment goals is the essential ethical, professional, scientific, and clinical goals of physicians. Using "affirming" treatments on minors violates this essential principle by using experimental treatments on vulnerable populations without properly informing them of the actual risks and limitations of the treatments.[126]

105. It is now universally agreed that medical and psychotherapy patients have a right to proper informed consent. Professional ethics codes, licensing rules and regulations, hospital rules and regulations, state and federal laws, and biomedical conventions and declarations all protect patients' right to informed consent discussions of the risks and benefits of proposed treatments and alternative treatments including no treatment.[127]

106. Essential requirements for informed consent include the ability of the patient or study subject to understand the proposed procedure, full disclosure of known and potential risks and benefits, discussion of alternative treatments, and freedom to act voluntarily. This information is presented verbally and in written form with allowance of sufficient time for the patient to ask

[126] See A. R. Jonsen et al., Clinical Ethics: A Practical Approach to Ethical Decisions in Clinical Medicine (4th ed. 1998).

[127] See *id.* ("Informed consent is defined as the willing acceptance of a medical intervention by a patient after adequate disclosure by the physician of the nature of the intervention, its risks, and benefits, as well as of alternatives with their risks and benefits."). See also A. L. Katz et al., Informed Consent in Decision-Making in Pediatric Practice, 138 Pediatrics e20161485 (2016) (reaffirmed in AAP Publications Reaffirmed, 151 Pediatrics e2023061452 (2023)).

questions and for the provider to assess adequate comprehension by the patient. It is well recognized that the signing of a formal consent form does not guarantee that informed consent has been obtained.

107. Several aspects of the care of individuals with gender dysphoria may substantially interfere with proper application of these foundational principles.[128] For adolescent children seeking medical gender affirmation, well-established limitations in decision-making ability raise serious concerns about their ability to consent to hormonal and surgical interventions. Adolescents have a known tendency to engage in risky behaviors, exercise poor impulse control, and show frequent failure to appreciate long-term consequences of current choices.[129]

108. For example, the ability of a child to understand implications for future fertility while still developmentally immature can pose a significant barrier to meeting the criterion of appreciating decision consequence. Children are often unlikely to be capable of giving truly informed consent, particularly when it comes to hormonal or surgical treatments that can result in lifelong sterility.[130] Adolescents' inability to adequately weigh potential short-term benefits against long-term risks seems supported by the observation that few adolescents express concern over loss of fertility even when directly told of the potential sterilizing effect of medical intervention.[131]

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[128] P. S. Appelbaum et al., Assessing Patients' Capacities to Consent to Treatment, 319 N. Engl. J. Med. 1635 (1988) (correction issued in Correction, 320 N. Engl. J. Med. 748 (1989)).
[129] Neuroscientists have found that the adolescent brain is too immature to make reliably rational decisions. S-J. Blakemore et al., Decision-Making in the Adolescent Brain, 15 Nature Neurosci. 1184 (2012); B. J. Casey et al., The Adolescent Brain 1124 Annals N.Y. Acad. Scis. 111 (2008).
[130] See C. F. Geier, Adolescent cognitive control and reward processing: Implications for risk taking and substance use, 64 Hormones and Behavior 333 (2013).
[131] L. Nahata et al. (2017), Low Fertility Preservation Utilization, 61 J. Adolesc. Health, at 40.

109. Similarly, individuals with transgender identity who also have clinical depression or other serious psychiatric comorbidity may have limited capacity to objectively weigh proposed clinical interventions with potentially irreversible consequences and would therefore fail to meet psychological abilities criteria.[132]

110. In addition, a study subject's underlying belief that he or she was born in the wrong body is the primary reason for seeking medical intervention. Thus, any challenge to this underlying premise is seen as a threat to the affected individual. Under such conditions, an individual will find it difficult, if not impossible, to give truly informed consent.

111. A model relying on parental consent with child assenting to affirmative medical interventions does not remove concerns about the difficulty in obtaining truly informed consent. Since many of the long-term outcomes of gender-affirming interventions are unknown, prospective patients are being asked to consent without sufficient knowledge of inherent risk versus benefit. Without understanding that nearly all adolescents who are put on puberty blockers will proceed to cross-sex hormones, with many subsequently opting for gender-affirming surgeries, focus on gaining consent for this first stage of the affirmative model is difficult if not impossible.

112. Parents are often told by gender affirmation activists or providers that the failure to allow a gender dysphoric child to medically transition will result in suicide. These "threats" ignore data that challenge this biased assumption.[133]

113. While any cases of suicide are of utmost concern, suicide rates in children with sex-discordant gender identity must be put in context of overall suicidality in the pediatric population

[132] H. Helmchen, Ethics of Clinical Research with Mentally Ill Persons, 262 Eur. Archs. Psychiatry and Clin. Neurosci. 441 (2012).
[133] See D'Angelo et al., One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria, 50 Archs. Sex. Behav. 7 (2021).

independent of gender dysphoria. When considered in this context, the rates of suicidal ideation and attempt in transgender adolescents are similar to those found in adolescents without gender dysphoria who present for psychological care.[134] Furthermore, it is necessary to critically assess, with rigorous scientific data, whether gender affirming medical interventions succeed in preventing suicides. While long-term data are not available for pediatric patients, the adult literature consistently reports continued elevated suicidality after undergoing gender affirming medical interventions.[135] In considering the population-based study in Sweden by Dhejne and colleagues,[136] it is not possible to draw conclusions on the effect of gender affirming interventions on suicide outcome since it was not a controlled study. Nevertheless, the observation that completed suicide rates following such interventions were 19-fold above the background population clearly demonstrates that gender affirming medical care did not fix the problem of suicide.

114. Researchers have noted that in the "affirming" context, "the informed consent process rarely adequately discloses" either "the uncertain permanence of a child's or an adolescent's gender identity" or "the uncertain long-term physical and psychological health outcomes of gender transition."[137] Levine et al. recently noted the following major deficiencies in the informed consent process under existing "affirming" guidelines and approaches:

- "High rate of desistance/natural resolution of gender dysphoria in children is not disclosed";
- "Implications of very low-quality evidence that underlies the practice of pediatric gender transition are not explained"; and

[134] M. Aitken et al., Self-Harm and Suicidality in Children Referred for Gender Dysphoria, 55 J. Am. Acad. Child & Adolesc. Psychiatry, 513 (2016).
[135] N. Adams et al., Varied Reports of Adult Transgender Suicidality: Synthesizing and Describing the Peer-Reviewed and Gray Literature, 2 Transgender Health 60 (2017).
[136] C. Dhejne et al., Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden, 6 PLOS ONE e16885 (2011).
[137] S. B. Levine et al., Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults, 48 J. Sex & Marital Therapy 706 (2022).

- "The question of suicide is inappropriately handled."[138]

As discussed above, the informed consent process for "affirming" treatments is further "limited by" "erroneous professional assumptions" and "poor quality of the initial evaluations."[139]

115. Given the low quality of scientific evidence available regarding the effects of puberty blockers and cross-sex hormones on children with sex-discordant gender identity as discussed below in this report, the relevant scientific community recognizes that medical gender affirmation of adolescent children remains experimental.[140] Using experimental procedures on uninformed, vulnerable patients is unethical and improper. Some of the most tragic chapters in the history of medicine include violations of informed consent and improper experimentation on patients using methods and procedures that have not been tested and validated by methodologically sound science — such is the case with the gender transition industry. The infamous Tuskegee studies, Nazi and Imperial Japanese wartime experiments, lobotomies (e.g., Dr. Egas Moniz received the 1949 Nobel Prize in Medicine for inventing lobotomies as a "treatment" for schizophrenia[141]), recovered memory therapy, multiple personality disorders, rebirthing therapy,[142] coercive

[138] *Id.* at 711, 712, 713.
[139] *Id.* at 706 (Abstract).
[140] Ludvigsson JF et al. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. Acta Paediatr. 2023 Apr 17. Epub ahead of print; "Recommendation of the Council for Choices in Health Care in Finland (PALKO/COHERE Finland): Medical Treatment Methods for Dysphoria Related to Gender Variance In Minors," PALVELUVALIKOIMA, p. 8.
[141] See Bengt Jansson, Egas Moniz: Controversial Psychosurgery Resulted in a Nobel Prize, NobelPrize.org (Oct. 29, 1998), https://www.nobelprize.org/prizes/medicine/1949/moniz/article/ (last visited Apr 11, 2023).
[142] See, e.g., M. Janofsky, Girl's Death Brings Ban on a Kind of Therapy, The New York Times, Apr. 18, 2001, https://www.nytimes.com/2001/04/18/us/girl-s-death-brings-ban-on-a-kind-of-therapy.html (last visited Apr 11, 2023); see also P. Lowe, Rebirthing team convicted: Two therapists face mandatory terms of 16 to 48 years in jail, Rocky Mountain News, Apr. 21, 2001.

holding therapy,[143] and other tragic examples should serve as a stark warning to medical providers to properly protect the rights of patients and their families to a proper informed consent process and to not be subjected to experimental, unproven interventions.

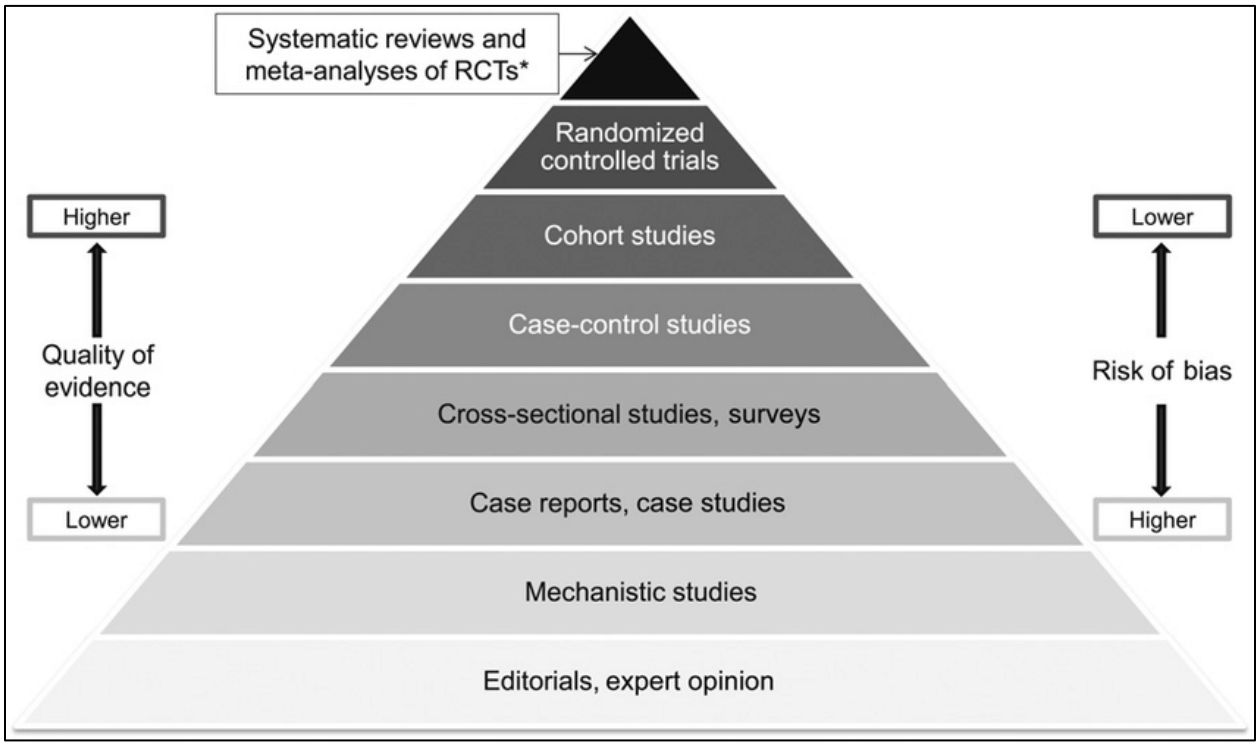
EXISTING LITERATURE AND ITS LIMITATIONS

116. Before turning to the existing literature on gender dysphoria and its treatments, it is important to understand the varying types of studies conducted in this and other medical fields, as well as the general approach to scientific testing. Appropriate testing of medical and other scientific hypothesis requires proper study design. First, the researcher formulates a hypothesis as to whether there is a difference — a cause and effect relationship — from the studied intervention. The study starts by assuming the "null hypothesis" — there is no difference — and then one looks for evidence sufficient to disprove the null hypothesis. When conducting the study, statistical significance is of central importance, for it states the likelihood that the observation would exist if the null hypothesis were true. Only if there is a very small likelihood that the null hypothesis is true is it generally appropriate to treat a study as providing evidence that the null hypothesis is, in fact, false. Accordingly, if a study finding does not reach statistical significance, it would be improper to use the finding as a rejection of the null hypothesis.

117. Case reports or experts' opinions are recognized as the lowest level of evidence. Those are based upon general experiences, not scientific testing. They can be useful for generating novel hypotheses, which can then be tested through experimental testing to establish if there are cause/effect relationships. Next up on the pyramid of quality of evidence would be, for example, cross-sectional studies that are done where one looks at a condition at one point in time. One can

[143] See J. Hyde, Holding therapy appears finished, Deseret News (Feb. 23, 2005), https://www.deseret.com/2005/2/13/19877054/holding-therapy-appears-finished (last visited Apr 11, 2023).

merely infer associations from these types of studies. Randomized longitudinal studies can permit, to some extent, the elimination of unrecognized variables that may distort the results. The highest part of the evidence-based pyramid (for individual studies) is randomized controlled trials, in which the investigator attempts to control all aspects of the study with the exception of the independent variable that is being tested. When done properly, this type of study can provide strong evidence of causation. The following illustrates this pyramid:[144]



118. Since the "affirming" model of treating transgender children — as summarized by the WPATH and Endocrine Society guidelines discussed above — are relatively new, long-term outcomes are unknown. Evidence presented as support for short-term reductions in psychological

[144] Image available at https://www.researchgate.net/figure/Hierarchy-of-evidence-pyramid-The-pyramidal-shape-qualitatively-integrates-the-amount-of_fig1_311504831. For original source, see E. A Yetley et al., Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: report from a joint US-/Canadian-sponsored working group, 105 Am. J. Clin. Nutrition 249S, 259S (2017).

distress following social transition in a "gender-affirming" environment remains inconclusive. Multiple potential confounders are evident. The most notable deficiencies of existing research are the absence of proper control subjects and lack of randomization in study design.[145] No randomized control trials have been performed, and the existing longitudinal studies have serious limitations — most significantly, that they follow cohorts of patients in a non-controlled, unrandomized manner. This design severely limits any conclusions that can be drawn.

119. Moreover, many studies find no improvement — or negative effects — from "affirming" care. For instance, a 2020 British study (Carmichael et al.[146]) found "no evidence of change in psychological function with GnRHa treatment as indicated by parent report (CBCL) or self-report (YSR) of overall problems, internalising or externalising problems or self-harm."[147] Puberty blockers used to treat children aged 12 to 15 who had severe and persistent gender dysphoria had no significant effect on their psychological function, thoughts of self-harm, or body image.[148] However, as expected, the children experienced reduced growth in height and bone strength by the time they finished their treatment at age 16.[149]

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[145] See P. W. Hruz, Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria, 87 Linacre Quarterly 34 (2020).

[146] P. Carmichael et al., Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK, 16 PLOS ONE e0243894, *1, *19 (2021). The acronyms CBCL and YSR refer to Child Behavior CheckList and Youth Self-Report, respectively. *Id.* at Abstract. See also H. Cass, The Cass Review, Independent review of gender identity services for children and young people: Interim report, Feb. 2022, at 31 and n.27, https://cass.independent-review.uk/wp-content/uploads/2022/03/Cass-Review-Interim-Report-Final-Web-Accessible.pdf.

[147] P. Carmichael et al. (2020), Short-term outcomes of pubertal suppression, 16 PLOS ONE e0243894, at *19.

[148] *Id.* at *18, *19.

[149] *Id.*

120. The widely respected Cochrane Review examined hormonal treatment outcomes for male-to-female transitioners over 16 years.[150] They found "insufficient evidence to determine the efficacy or safety of hormonal treatment approaches for transgender women in transition."[151] Thus, decades after the first transitioned male-to-female patient, quality evidence for the benefit of transitioning remains lacking.

121. Although appropriate caution is warranted in extrapolating the outcomes observed from prior studies with current treatments, adults who have undergone social transition with or without surgical modification of external genitalia continue to have rates of depression, anxiety, substance abuse, and suicide far above the background population.[152]

122. Given the low quality of scientific evidence currently available regarding the relative risk versus benefit of gender-affirming medical interventions, existing evidence that suicidality remains markedly elevated after engaging in this therapeutic approach, and a general failure to directly test the benefits of psychological intervention to alleviate suffering in people who experience sex-discordant gender identity, before offering gender affirming care as a standard treatment there is an ethical imperative to conduct clinical trials to assess the validity of alternate hypotheses for effective treatment. Dismissal of randomized controlled trials rests upon an erroneous portrayal of clinical trial design. While it may be true that prospective research subjects would reject enrollment in a trial comparing affirmative care with no care, proper discussion of the inherent risk

[150] See C. Haupt et al., Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women, 2020 Cochrane Database of Systematic Revs., Issue 11, Art. No. CD013138 (2020).
[151] *Id.* at 2.
[152] See N. Adams et al., Varied Reports of Adult Transgender Suicidality: Synthesizing and Describing the Peer-Reviewed and Gray Literature, 2 Transgender Health 60, 60-75 (2017). See also C. Dhejne et al. (2011), Long-Term Follow-Up of Transsexual Persons, 6 PLOS ONE e16885.

of gender affirming interventions, the lack of data showing long term resolution of suicidal ideation, and the goal of alleviating dysphoria through alternate means can provide reasonable expectation of enrolling a sufficient number of study subjects.

123. The 2015 study by Costa et al.[153] provides preliminary evidence that psychotherapy alone is associated with improved mental health. It is important to note that in this study comparing subjects that received psychological support alone versus those who received psychological support together with pubertal blockade, both study groups had significantly improved psychosocial function (CGAS) from baseline. Importantly, there was no statistical difference in CGAS scores between the two study groups throughout the study.[154] A lack of significant difference means that one cannot reject the null hypothesis because any observed differences could be due to random chance. Both groups had final CGAS scores in the 61-70 range, which reflects "some difficulty in a single area but generally functioning well."[155] The magnitude of difference between the CGAS scores at the end of the study was 5 points on a 100-point scale.[156] Of high interest would be an attempt to replicate this study in a randomized manner to better ascertain a causal relationship between psychotherapy and mental health.

I. Change in Patient Population

124. One important (and contentious) issue requiring more study is the recent trend of adolescent female to male gender discordant patients. In the United Kingdom, where centralized

[153] R. Costa et al., Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria, 12 J. Sexual Med. 2206 (2015) (using the Utrecht Gender Dysphoria Scale (UGDS) and the Children's Global Assessment Scale (CGAS) as main outcome measures).
[154] *Id.* at 2206.
[155] D. Shaffer, A Children's Global Assessment Scale (CGAS), 40 Archs. Gen. Psychiatry 1228 (1983).
[156] R. Costa et al. (2015), Psychological Support, Puberty Suppression, and Psychological Functioning, 12 J. Sexual Med. at 2212 (Table 2).

medical care provides data to track health care phenomenon, the number of adolescent girls seeking sex transitioning exploded over 4,000% in the last decade. Similarly, in the United States, where we lack the same kinds of centralized health care data, it has been reported that, in 2018, 2% of high school students identified on surveys as "transgender" — this is 200 times greater response, a 20,000% increase — over reports during past decades which showed a rate of only .01%.[157]

125. Along with this increase in transgender patients and identifiers has come a radical and recent transformation of the patient population from early onset males to rapid onset adolescent girls. Currently the majority of new patients with sex-gender discordance are not males with a long, stable history of gender dysphoria since early childhood — as they were for decades, and under the Dutch protocols — but instead adolescent females with no documented long-term history of gender dysphoria. One might say, as Dr. Lisa Littman has theorized,[158] that these females experienced "rapid onset" transgender identification.

126. This recent change in the typical patient raises questions about our understanding of the origins of transgender identity. For instance, a genetics or "immutable" theory of transgender identity cannot explain the rapid expansion of new gender dysphoria cases (a 4,000% to 20,000% increase), given that our genome is simply not changing that fast. Nor can that theory explain the explosion of adolescent females presenting with gender dysphoria. A "brain structures" theory has only weak medical evidence, and it also cannot explain the rapid expansion of

[157] See M. M. Johns et al., Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students — 19 States and Large Urban School Districts, 2017, 68 MMWR Morb. Mortal. Wkly. Rep. 67 (2019).
[158] See L. Littman, Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria, 13 PLOS ONE e0202330 (2018); Erratum in L. Littman, Correction: Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria, 14 PLOS ONE e0214157 (2019).

new gender dysphoria cases. As for the theory that increased social acceptance is leading many people who were transgender all along to identify as such to their medical providers, this theory fails to explain why the rate of increase in males and older women transitioning has not kept pace with that for adolescent females. It also does not explain why many adolescent females are found transitioning along with their "social peer group clusters."

II. Methodological Problems with "Affirming" Literature

127. The published literature relied on to advocate for the use of puberty blockers, cross-sex hormones, and gender-affirming surgeries in minors consists almost entirely of studies with major methodological limitations.[159] As detailed next, these include:

- Significant recruitment biases, including internet-based convenience sampling;
- Relatively small sample sizes for addressing a condition that is likely to be multi-factorial;
- Short-term follow-up;
- Lack of randomization to different treatment arms;
- Failure to consider alternate hypotheses;
- Failure to include proper control groups;
- Reliance on cross sectional sampling that may identify associations, but cannot establish causal relationships between intervention and outcome;
- A high rate of patients lost to follow up in longitudinal analyses, which is relevant to questions of regret, desistance, and completed suicide;
- Biased interpretation of study findings with a goal of validating *a priori* conclusions rather than seeking evidence to disprove the null hypothesis; and
- Ignoring starkly contradictory research documenting the lack of effectiveness of "transitioning" procedures, the low quality of research in this area, and the ongoing contentions and disagreements over this highly controversial, experimental medical field.

128. Some or all of these methodological and statistical flaws are present in the following studies, which are commonly relied on by advocates of "affirming" treatments. This list is not

[159] See generally P. W. Hruz (2020), Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria, 87 Linacre Quarterly, at 34.

exhaustive but is rather presented to demonstrate the serious scientific deficiencies in the published literature related to the care of individuals who experience sex-discordant gender identity.

The Bränström Long-Term Treatment Outcome Study: The historic Bränström study[160] is a long-term treatment outcome research investigation testing the effects of hormonal and surgical "transitioning" treatments on patients. Ultimately, but only after the authors' initial findings had come under public scrutiny,[161] this study found no reliable benefits from these treatments.[162] In addition, the study suggested *increased* suicide attempts and anxiety disorders following the "gender transitioning" treatments.[163]

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[160] R. Bränström et al., Reduction in Mental Health Treatment Utilization Among Transgender Individuals After Gender-Affirming Surgeries: A Total Population Study, 177 Am. J. Psychiatry 727 (2020). See also Correction to Bränström and Pachankis, 177 Am. J. Psychiatry 734 (2020).

[161] N. H. Kalin, Reassessing Mental Health Treatment Utilization Reduction in Transgender Individuals After Gender-Affirming Surgeries: A Comment by the Editor on the Process, 177 Am. J. Psychiatry 764 (2020) (writing on behalf of the Journal to announce a correction and an addendum published as a result of additional research requested and undertaken in response to the criticism of the Bränström study). See, e.g., A. Van Mol et al., Gender-Affirmation Surgery Conclusion Lacks Evidence, 177 Am. J. Psychiatry 765 (2020) (Letter to the Editor); A. Van Mol et al., Correction: Transgender Surgery Provides No Mental Health Benefit, Public Discourse, Sept. 13, 2020, https://www.thepublicdiscourse.com/2020/09/71296/ (last visited Apr 11, 2023). See also S. B. Levine, Reflections on the Clinician's Role with Individuals Who Self-identify as Transgender, 50 Archs. Sex Behav. 3527, 3530 (2021).

[162] See A. van Mol et al. (2020), Gender-Affirmation Surgery Conclusion Lacks Evidence, 177 Am. J. Psychiatry at 765 (Letter to the Editor). See also N. H. Kalin (2020), Reassessing: A Comment by the Editor on the Process, 177 Am. J. Psychiatry at 764; SEGM, Correction of a Key Study: No Evidence of "Gender-Affirming" Surgeries Improving Mental Health, https://segm.org/ajp_correction_2020 (Aug. 30, 2020).

[163] See, e.g., H. Anckarsäter et al., Methodological Shortcomings Undercut Statement in Support of Gender-Affirming Surgery, 177 Am. J. Psychiatry 764 (2020) (Letter to the Editor); A. van Mol et al., Gender-Affirmation Surgery Conclusion Lacks Evidence, 177 Am. J. Psychiatry 765 (2020) (Letter to the Editor); W. J. Malone et al., Calling Into Question Whether Gender-Affirming Surgery Relieves Psychological Distress, 177 Am. J. Psychiatry 766 (2020) (Letter to the Editor); M. Landén, The Effect of Gender-Affirming Treatment on Psychiatric Morbidity Is Still Undecided, 177 Am. J. Psychiatry 767, 767-68 (2020) (Letter to the Editor); A. Wold, Gender-Corrective Surgery Promoting Mental Health in Persons With Gender Dysphoria Not Supported by Data Presented in Article, 177 Am. J. Psychiatry 768 (2020) (Letter to the Editor) (noting that "among the

Of note, significant research errors suggested that the authors had initially attempted to manipulate and misreport the findings of the study.[164] After publication of the original article in October 2019, "letters containing questions on the statistical methodology employed in the study led the [American Journal of Psychiatry] to seek statistical consultations."[165] According to the Journal, "[t]he results of these consultations were presented to the study authors," who on request "reanalyzed the data."[166] That reanalysis led the authors to recant their initial misreporting, as "the results demonstrated no advantage of surgery in relation to subsequent mood or anxiety disorder-related health care visits or prescriptions or hospitalizations following suicide attempts."[167] And the Bränström study at no point showed any advantages from hormonal treatments in improving mental health outcomes.[168]

Thus, the Bränström study is devoid of any solid indication that medical interventions would objectively improve medical or mental health outcomes for transgender persons. Furthermore, because neither the original study nor the subsequent correction provide any statistically

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individuals examined in the study, the risk of being hospitalized for a suicide attempt was 2.4 times higher if they had undergone gender-corrective surgery than if they had not.").

[164] See, e.g., H. Anckarsäter et al. (2020) Methodological Shortcomings, 177 Am. J. Psychiatry at 764-65); D. Curtis, Study of Transgender Patients: Conclusions Are Not Supported by Findings, 177 Am. J. Psychiatry 766 (2020); A. van Mol et al. (2020), Gender-Affirmation Surgery Conclusion Lacks Evidence, 177 Am. J. Psychiatry at 765-66. See also A. Ring et al., Confounding Effects on Mental Health Observations After Sex Reassignment Surgery, 177 Am. J. Psychiatry 768, 768-69 (2020) (Letter to the Editor) (noting that "the same data [used in the Bränström study] may be modeled in a way that leads to the opposite conclusion" of that reached by Bränström study.).

[165] Correction to Bränström and Pachankis, 177 Am. J. Psychiatry 734 (2020).

[166] *Id.*

[167] *Id.*

[168] R. Bränström et al. (2020), Reduction in Mental Health Treatment Utilization, 177 Am. J. Psychiatry at 727. See also D. Curtis, Study of Transgender Patients: Conclusions Are Not Supported by Findings, 177 Am. J. Psychiatry 766 (2020) (Letter to the Editor) (stating that the Bränström study "does not demonstrate that either hormonal treatment or surgery has any effect on this morbidity.").

significant support for hormone treatment, the Bränström study has done nothing to close any of what the Cass Review, a formal independent review of gender identity services in the United Kingdom, has described as existing "gaps in the evidence base for hormone treatment" of minors.[169] Meanwhile, as discussed later in this report, several factors, including increased caution among some care providers, are resulting in a profound collapse of support for these experimental procedures across Europe, most notably in clinics providing treatment for minors.[170]

A 2011 Dutch study by De Vries et al.[171] is often cited to support longitudinal evidence of benefit from pubertal blockade. Although the study found slight improvements in mood and the risk of behavioral disorders with pubertal blockade over baseline, the study included no control group, and all 70 participants received ongoing psychological support. Thus, the authors were unable to determine the basis of the limited observed improvement. The authors acknowledge that psychological support or other reasons may have contributed to (or wholly caused) this observation. By the very nature of the trial, at best the study can provide a rationale for doing further studies that could show whether "affirming" interventions provide a benefit. The study does not (and cannot) answer the central question: whether the administration of puberty blockers is the solution to the problem and whether alternative approaches that do not carry the same risks relative to purported benefits (e.g., psychological interventions) may have the same or superior benefits.

Moreover, there remain questions about the extent to which the protocol used in these early Dutch studies may be relevant to the patient population presenting today. For decades transgender patients were mostly older adults or very young boys. As noted, over the last few years, a tsunami

[169] H. Cass (2022), The Cass Review — Interim Report, at 23.
[170] See, e.g., infra International Responses, ¶¶ 134 et seq.
[171] A. L. C. de Vries et al., Puberty Suppression in Adolescents With Gender Identity Disorder: A Prospective Follow-Up Study, 8 J. Sexual Med. 2276 (2011).

of teenaged girls has flipped the demographic ratio of transgender patients — now up to 7:1 for teen girls relative to teen boys. The newly presenting cases are vastly overrepresented by adolescent females, the majority of whom also have significant mental health problems and neurocognitive comorbidities such as autism-spectrum disorder or ADHD.[172] Furthermore, estimates of gender-dysphoria transgenderism are rocketing upwards from 1 in 10,000 to, in youth, "as high as 9%."[173] This unexplained, radical transformation of patient demographics raises questions about the applicability even of the limited existing literature on this issue, particularly as to the Dutch protocol. Dr. Thomas Steensma, a prominent investigator of the Dutch protocol — the original model for transitioning treatments — has recently noted that "[w]e don't know whether studies we have done in the past can still be applied to this time,"[174] specifically because of the unexplained surge in female adolescents reporting gender dysphoria. "Many more children are registering, but also of a different type . . . Suddenly there are many more girls applying who feel like a boy."[175] He concluded with the warning that "[w]e conduct structural research in the Netherlands. But the rest of the world is blindly adopting our research."[176]

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[172] See N. M. de Graaf et al., Reflections on emerging trends in clinical work with gender diverse children and adolescents, 24 Clin. Child Psychol. and Psychiatry 353 (2019).
[173] See K. M. Kidd et al., Prevalence of Gender-Diverse Youth in an Urban School District, 147 Pediatrics e2020049823 (2021).
[174] See B. Tetelepta, More research is urgently needed into transgender care for young people: "Where does the large increase of children come from?," Voorzij, Feb. 26, 2021, available at https://www.voorzij.nl/more-research-is-urgently-needed-into-transgender-care-for-young-people-where-does-the-large-increase-of-children-come-from/ (last visited Apr 11, 2023) (translation from B. Tetelepta, Dringend meer onderzoek nodig naar transgenderzorg aan jongeren: 'Waar komt de grote stroom kinderen vandaan?,' Algemeen Dagblad, Feb. 27, 2021, available at https://www.ad.nl/nijmegen/dringend-meer-onderzoek-nodig-naar-transgenderzorg-aan-jongeren-waar-komt-de-grote-stroom-kinderen-vandaan~aec79d00/ (last visited Apr 11, 2023)).
[175] *Id.*
[176] *Id.*

A 2014 follow-up study by De Vries et al.[177] encompassed 55 of the original 70 patients; 15 were lost to follow-up or not included. It has the same limitations that were present in assessing the original 2011 study, including a carefully selected patient population that is not representative of the broader population, especially now. Having a longer study does not obviate the limitations of the study design in making a conclusion that can be applied to the gender clinics that are operating in the United States.

In addition to the concerns of the Dutch studies already exposed, "[t]he linchpin result of the Dutch studies is the reported *resolution of gender dysphoria*, as measured by the Utrecht Gender Dysphoria Scale (UGDS)."[178] The UGDS is a tool developed in the mid-1990s to assess the degree of gender dysphoria experienced by research subjects with separate surveys for male and female subjects.[179] Yet, as several researchers (E. Abbruzzese et al.) recently explained, the observed "drop was an artifact of switching the scale from 'female' to 'male' versions (and vice versa) before and after treatment, prompting a problematic reversal in the scoring."[180] "The *same* gender dysphoric individual, effectively answering the *same* question (albeit linguistically inverted)" — e.g., "Every time someone treats me like a girl [or boy] I feel hurt" — "results in either the maximum or the minimum 'gender dysphoria' score — depending on which sexed version of the scale was used."[181] Thus, because researchers used different scales of the UGDS before and

[177] A. L. C. de Vries et al., Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment, 134 Pediatrics 696 (2014).
[178] E. Abbruzzese et al., The Myth of "Reliable Research" in Pediatric Gender Medicine: A critical evaluation of the Dutch Studies—and research that has followed, J. Sex & Marital Therapy, Jan. 2, 2023, at 1, 7-8.
[179] Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. J Am Acad Child Adolesc Psychiatry. 36(2):263-71 (1997); .
[180] *Id.* at 1, 8.
[181] *Id.* at 8.

after treatment, "it is impossible to determine if [the result shows] a real difference in gender dysphoria between groups or if this is an artifact of measurement error."[182] Indeed, if anything, "[t]he fact that after gender reassignment, the UGDS scores were low on the opposite-sex scale indicates that the subjects would have scored high on the natal sex scale, which corresponds to a *persistence in transgender identity*."[183] This, of course, is the opposite result purportedly reached by the 2014 De Vries study.

The 2018 paper by Wiepjes et al.[184] is a retrospective review of records from all patients of the Center of Expertise on Gender Dysphoria gender clinic in Amsterdam from 1972-2015. While the study appears to report on the regret rates among a large cohort of adolescents (812) and children (548),[185] regret is only reported for children and adolescents who had undergone gonadectomy once over 18 years of age.[186] Of the adolescents, 41% started puberty suppression. Of those who started GnRH agonists, only 2% stopped this intervention (meaning that 98% of those who started puberty suppression progressed to cross-sex hormone therapy).[187] An additional 32%, having already completed puberty, started cross-sex hormone therapy without use of a GnRH agonist.[188] Classification of regret was very stringent, requiring physician documentation of patient verbalized regret after gonadectomy and start of sex-concordant hormones to treat the

[182] *Id.* at 9 (internal quotation and citation omitted).
[183] *Id.* at 10 (emphasis in original).
[184] C. M. Wiepjes et al., The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets, 15 J. Sexual Med. 582 (2018).
[185] *Id.* at 584 (Table 1).
[186] *Id.* at 585, 587. See also *id.* at 582 (Abstract).
[187] *Id.* at 585 ("Of adolescents, 41.0% started PS, whereas only 1.9% of these adolescents stopped PS and did not start HT (Table 1).").
[188] *Id.*

iatrogenic hypogonadism.[189] This means there are significant limitations to the conclusions that can be drawn from this paper. There is no discussion in the paper regarding adolescent regret of use of puberty blockers, cross-sex hormones, or mastectomies. Importantly, 36% of patients were lost to follow up.[190] This is notable given that gonadectomy iatrogenically induces the pathologic state of primary hypogonadism. Affected patients have a lifelong dependency for exogenously administered sex-steroid hormones, and thus an acute need for ongoing follow-up. Their failure to return to the physicians who provided gender-affirming interventions raises serious questions about their outcome. It is reasonable to hypothesize that some may have experienced regret or completed suicide. Yet due to missing data, their fate remains unknown. It is also significant that the average time to regret was 130 months.[191] The authors themselves acknowledge that it may be too early to predict regret in patients who started hormone therapy in the past 10 years.[192]

The 2022 Tang et al. paper[193] is a retrospective chart review that aims to assess surgical outcomes in adolescents aged 12-17 years who underwent bilateral mastectomy for gender dysphoria from 2013-2020 within the Kaiser Permanente Health Care System in Northern California. The authors identified 209 subjects who had undergone this procedure. Of this group, only 137 had follow-up data more than 1 year after surgery. Complications were found in 7.3% with two of the subjects expressing regret within this interval. Despite claims to the contrary, this study documents that surgeries are being performed on adolescents with gender dysphoria as early

[189] *Id.* at 583-84, 587 (with columns in Table 4 indicating the type of detransitions for each patient listed and the specific reversal treatments undertaken for each patient listed).
[190] *Id.* at 589.
[191] *Id.* at 589.
[192] *Id.* at 589.
[193] Tang A, Hojilla JC, Jackson JE, Rothenberg KA, Gologorsky RC, Stram DA, Mooney CM, Hernandez SL, Yokoo KM. Gender-Affirming Mastectomy Trends and Surgical Outcomes in Adolescents. Ann Plast Surg. 2022 May;88(4 Suppl):S325-S331.

as 12 years of age. There are several serious limitations of this study. This includes a retrospective study design, which as noted above cannot establish a causal relationship between intervention and outcome. There is also lack of outcome data on 82 of the 209 subjects (39%) with potential for bias in the outcome of missing subjects. Furthermore, the follow-up was very short (mean of 2.1 years). As noted above for the Wiepjes study,[194] this timeframe is insufficient to ascertain regret.

The 2018 Olson-Kennedy et al. paper[195] presents the results of a survey of biologically female patients with male gender identity at the lead author's institution using a novel rating system for "chest dysphoria" created by the study authors.[196] There were an equal number (68) of nonsurgical and post-surgical subjects surveyed.[197] Those who had undergone bilateral mastectomies were reported to have less chest dysphoria than those who did not receive this intervention.[198] Limitations of this study include convenience sampling of nonsurgical study subjects with high potential for selection bias. As in the above studies, cross-sectional design precludes establishment of a causal relationship between intervention and outcome measures. The primary outcome measure was not assessed by a validated assessment tool. Test validation is particularly relevant in assessing adolescent questionnaires due to a variety of cognitive and situational factors in this population.[199] Rigorous validation methods have been previously used in several other established

[194] Wiepjes et al., at 589.
[195] J. Olson-Kennedy et al., Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts, 172 JAMA Pediatrics 431 (2018).
[196] *Id.* at 432.
[197] *Id.* at 431.
[198] *Id.* at 431 (Abstract).
[199] See N. D. Brener et al., Assessment of factors affecting the validity of self-reported health-risk behavior among adolescents: evidence from the scientific literature, 33 J. Adolesc. Health 436 (2003).

questionnaires addressing adolescent self-perception.[200] Furthermore, as noted in the above studies, the short follow-up time (about 2 years) is insufficient to assess an outcome (regret) that has been shown to occur a decade after the intervention.[201]

A 2019 study by Allen et al.[202] considered suicidality after cross-sex hormones. It was limited by a very small patient population (47), had no control group, had a short follow-up period (mean < 1 year), and again ignored that patients receiving the interventions also received psychological support.

A 2019-2020 study by Turban et al. in JAMA Psychiatry[203] aimed to consider "recalled exposure to gender identity conversion efforts [GICE] (ie, psychological interventions that attempt to change one's gender identity from transgender to cisgender) associated with adverse mental

[200] See N. Palenzuela-Luis et al., Questionnaires Assessing Adolescents' Self-Concept, Self-Perception, Physical Activity and Lifestyle: A Systematic Review, 9 Children 91 (2022).
[201] Wiepjes et al., at 589
[202] L. R. Allen et al., Well-being and suicidality among transgender youth after gender-affirming hormones, 7 Clin. Practice in Pediatric Psychol. 302 (2019).
[203] J. L. Turban et al., Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults, 77 JAMA Psychiatry 68 (2020) (originally posted online on September 11, 2019).

health outcomes in adulthood."[204] However, this paper has been repeatedly and pointedly criticized for a number of improper extrapolations and serious methodological defects,[205] several of which stem from its reliance on flawed data from the 2015 U.S. Transgender Survey (USTS).[206]

The USTS was an anonymous online survey conducted in the summer of 2015[207] and "is the largest survey examining the experiences of transgender people in the United States, with 27,715 respondents."[208] Anonymous surveys are not rigorous sources of evidence, and the data from this survey are compromised by numerous biases and irregularities. The 2015 USTS Report and Executive Summary were published by the National Coalition for Transgender Equality

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[204] *Id.* at 68.

[205] See, e.g., D'Angelo et al. (2021), One Size Does Not Fit All, 50 Archs. Sex. Behav., at 7; R. Byng et al., Misinterpretation of the findings of this study may limit safe, ethical treatment options for gender-questioning and gender-diverse people, Comment on J. L. Turban et al., Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults, 77 JAMA Psychiatry 68 (2020), Comment posted on Oct. 8, 2019, available at https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2749479; H. Horvath, A deeply flawed analysis, Comment on J. L. Turban et al., Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults, 77 JAMA Psychiatry 68 (2020), Comment posted on Oct. 6, 2019, available at https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2749479; J. Mason, Not all therapy is conversion therapy, Comment on J. L. Turban et al., Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults, 77 JAMA Psychiatry 68 (2020), Comment posted on Sept. 27, 2019, available at https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2749479. These three Comments on Turban's article at JAMA Psychiatry, the comments by Byng et al., H. Horvath, and J. Mason, shall collectively be referred to as "Three Comments on J. L. Turban, Associations (2019-2020), at 77 JAMA Psychiatry 68."

[206] 2015 U.S. Transgender Survey Report, 2022 U.S. Trans Survey, https://www.ustranssurvey.org/reports (last visited Apr 25, 2023).

[207] S. E. James et al., The Report of the 2015 U.S. Transgender Survey, 4, Washington, DC: National Center for Transgender Equality (2016), available at https://transequality.org/sites/default/files/docs/usts/USTS-Full-Report-Dec17.pdf (last visited Apr. 25, 2023) ("USTS 2015 Report").

[208] *Id.*

(NCTE).[209] Several authors of the USTS Report have been actively involved in policy work and legal advocacy at both the state and federal level, and in legislatures and courts.[210] More broadly, the USTS is currently supported by a coalition including several trans advocacy groups that, like the NCTE, are active in the realm of public policy.[211] In 2022, the USTS conducted another survey in partnership with several other trans advocacy organizations, and results are expected to be released later in 2023.[212] The current homepage for the USTS describes the 2022 survey as "the largest survey of trans people, by trans people, in the United States."[213]

The Turban et al. 2019-2020 JAMA Psychiatry study relying on the USTS survey tool has been criticized on account of several limitations and weaknesses of that survey tool — and resulting data — such as convenience sampling[214] and recruitment of patients through transgender advocacy organizations.[215] Furthermore, the USTS "sampling method's inadequacy"[216] renders it highly unlikely that the survey tool (and thus the Turban 2019-2020 study data) captures or adequately accounts for populations integral to this study and its conclusions, such as "the population

[209] S. E. James et al., USTS 2015 Report; S. E. James et al., Executive Summary of the Report of the 2015 U.S. Transgender Survey, 16, Washington, DC: National Center for Transgender Equality (2016), available at https://transequality.org/sites/default/files/docs/usts/USTS-Executive-Summary-Dec17.pdf (last visited Apr. 25, 2023).
[210] S.E. James et al. (2015), USTS 2015 Report, at 241-42.
[211] See 2022 U.S. Trans Survey, USTS Homepage (featuring logos from and hyperlinks to BTAC, the Black Trans Advocacy Coalition; the TransLatin@ Coalition; and NQAPIA, the National Queer Asian Pacific Islander Alliance).
[212] 2022 U.S. Trans Survey, 2022 U.S. Trans Survey, https://www.ustranssurvey.org (last visited Apr 25, 2023) (USTS Homepage); FAQ's, 2022 U.S. Trans Survey, https://www.ustranssurvey.org/faq (last visited Apr 28, 2023) (Who Conducts the USTS?).
[213] *Id.*
[214] See, e.g., Three Comments on J. L. Turban, Associations (2019-2020), at 77 JAMA Psychiatry 68.
[215] Three Comments on J. L. Turban, Associations (2019-2020), at 77 JAMA Psychiatry 68.
[216] H. Horvath, A deeply flawed analysis, Comment on J. L. Turban et al. (2019-2020), 77 JAMA Psychiatry 68.

whose earlier gender dysphoria was alleviated through cognitive behavioral therapy or other standard approaches,"[217] or "individuals exposed to GICE who subsequently adopted a gender identity concordant with their biological sex."[218] Another crucial defect is the failure of Turban et al. to "control for comorbid psychiatric illness, the greatest single predictor of suicidality."[219]

In their comment, Byng et al. concluded:

> [T]he authors underplay the serious methodological weaknesses, particularly the likely confounding effects of co-existing mental health problems. They then take this association and in the abstract and conclusion seek to imply causation. Hence, the findings could mislead frontline clinicians and public policymakers alike. [220]

D'Angelo et al.,[221] in their response to the Turban et al. 2019-2020 JAMA Psychiatry study, highlighted further limitations of the USTS survey tool.[222] These include demand bias (i.e., the good subject effect[223]), a high number of respondents who reported having not transitioned medically or socially (and reported no desire to do so in the future), and several data irregularities.[224]

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[217] *Id.*
[218] R. Byng et al., Misinterpretation of the findings, Comment on J.T. Turban et al. (2019-2020), 77 JAMA Psychiatry at 68.
[219] R. Byng et al., Misinterpretation of the findings, Comment on J.T. Turban et al. (2019-2020), 77 JAMA Psychiatry at 68. See also J. Mason, Not all therapy is conversion therapy, Comment on J. L. Turban et al. (2019-2020), 77 JAMA Psychiatry 68 ("Turban et al allowed a number of study limitations — including convenience sampling and failure to control for mental illness, a key predictor of suicidality — which should make any savvy reader wary of accepting the study conclusions about the harms of therapy aimed at alleviating GD.").
[220] R. Byng et al., Misinterpretation of the findings, Comment on J.T. Turban et al. (2019-2020), 77 JAMA Psychiatry at 68. See also H. Horvath, A deeply flawed analysis, Comment on J.T. Turban et al. (2019-2020), 77 JAMA Psychiatry at 68 ("It is surprising that so eminent a scholar as Dr. Turban did not perceive the methodological errors to which he was evidently susceptible in preparing his recent analysis of suicidality in transgender persons.").
[221] *Id.*
[222] *Id.* at 7. See J. L. Turban et al., Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults, 77 JAMA Psychiatry 68 (2020).
[223] A. L. Nichols et al., The Good-Subject Effect: Investigating Participant Demand Characteristics, 135 J. Gen. Psychol. 151 (2008).
[224] D'Angelo et al. (2021), One Size Does Not Fit All, 50 Archs. Sex. Behav., at 8.

One notable data irregularity was that a high number of USTS respondents reported that their age was exactly 18 years.[225] Another was that "information about treatments received does not appear to be accurate, as a number of [USTS] respondents reported the initiation of puberty blockers after the age of 18 years, which is highly improbable."[226] These irregularities raise serious questions about the reliability of the USTS data and therefore the reliability of conclusions based on that data.[227] Because the 2019-2020 Turban study in JAMA Psychiatry is founded on a data set from an anonymous survey replete with flaws such as bias and convenience sampling, and because the study fails to control for multiple population gaps in the survey data and multiple key variables (such as co-morbid psychological illness), its conclusions are unreliable and potentially misleading.

Additional flaws and limitations of the USTS 2015 Survey data are set forth below in this report's summaries of the Turban et al. 2020 Pediatrics study, the Almazan et al. 2021 study, and the 2022 Turban et al. study, all papers which relied substantially on the USTS data.[228]

Another 2020 study by Turban et al. in Pediatrics[229] is often cited as proof that pubertal blockade prevents suicide in transgender youth. But this study also used the same unreliable,

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[225] *Id.*
[226] *Id.* at 8 (internal citation omitted).
[227] See generally *id.* at 7-16.
[228] See infra discussion of the 2022 Turban et al. study. Also, further caution is warranted in evaluating the literature as the flawed data from the 2015 USTS may appear in other studies, including studies that have yet to be published. Upon request, the USTS makes the raw data from the 2015 survey available to researchers through the Inter-University Consortium for Political and Social Research (ICPSR). See Data Requests, 2022 U.S. Trans Survey, https://www.ustranssurvey.org/data-requests (last visited Apr 25, 2023). See also ICPSR, 2015 U.S. Transgender Survey (USTS) (ICPSR 37229), Version Date: May 22, 2019, https://www.icpsr.umich.edu/web/RCMD/studies/37229 (last visited Apr. 29, 2023).
[229] J. L. Turban et al., Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation, 145 Pediatrics e20191725 (2020). See also Erratum for TURBAN 2019-1725, 147 Pediatrics e2020049767 (2021).

biased sampling methodology, the 2015 USTS.[230] As stated in the paper, the authors considered "a cross-sectional online survey of 20,619 transgender adults aged 18 to 36 years" from the 2015 U.S. Transgender Survey.[231] In addition to the defects in the 2015 USTS anonymous online survey discussed above, there is no evidence of study subject identities, no way to assess for potential false subjects, and no medical diagnosis for entry into the survey. Also, the patient sample was compromised by ascertainment bias.[232] It is impossible for deceased persons, including those who have succumbed to suicide, to respond to an online survey necessary for their inclusion into the data set. No causation can be determined from this retrospective, cross-sectional design. Furthermore, the study apparently failed to even assess individuals who may have desisted or regretted transitions.[233] Thus, the study "does not include outcomes for people who may have initiated pubertal suppression and subsequently no longer identify as transgender."[234]

Turban's misleading claim of lower suicidal ideation for treated patients is based upon "lifetime suicidality."[235] It fails to recognize or acknowledge that the decision to provide puberty blockers was likely influenced by the mental health of the subjects at the time of presentation.[236]

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[230] *Id.* at *2-*3 and n.6.
[231] *Id.* at *1, *2-*3.
[232] P. W. Hruz, Suicidality in Gender Dysphoric Youth Offered Pubertal Blockade Remains Alarmingly High, Comment on Comment on J. L. Turban, Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation, 145 Pediatrics e20191725, Comment published on Jan. 26, 2020, available at https://publications.aap.org/pediatrics/article/145/2/e20191725/68259/Pubertal-Suppression-for-Transgender-Youth-and?autologincheck=redirected (last visited April 24, 2023).
[233] J. L. Turban et al. (2020), Pubertal Suppression, 145 Pediatrics e20191725, at *1-*8.
[234] *Id.* at *7.
[235] *Id.* at *4.
[236] M. Biggs, Comment on J. L. Turban, Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation, 145 Pediatrics e20191725, Comment published on Jan. 30, 2020, available at https://publications.aap.org/pediatrics/article/145/2/e20191725/68259/Pubertal-Suppression-for-Transgender-Youth-and?autologincheck=redirected (last visited April 24, 2023).

Specifically, the most seriously mentally ill patients would have been denied puberty blockers.[237] The study can only be understood in light of these limitations and confounding issues.

According to the study, those who received treatment with pubertal suppression, when compared with those who wanted pubertal suppression but did not receive it, had lower odds of lifetime suicidal ideation (adjusted odds ratio = 0.3; 95% confidence interval = 0.2-0.6).[238] In Table 3 of the paper, under "Suicidality (past 12 months)" reductions for suppressed group versus non-suppressed were seen for ideation (50.6% v 64.8%) and "ideation with plan" (55.6% v 58.2%).[239] However, it is important to note that differences in suicidal "ideation with plan and suicide attempt" and "attempt resulting for inpatient care" did not reach statistical significance.[240] When discussing the results of their study, the authors fail to mention this lack of statistical significance in two of the most serious measures and, instead, reference only suicidal ideation. It would be reasonable to be concerned from an observation of over 40% attempted suicide in the treated group that the intervention was unsuccessful in improving health.[241]

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[237] *Id.*
[238] J. L. Turban et al. (2020), Pubertal Suppression, 145 Pediatrics e20191725, at *1.
[239] *Id.* at *5.
[240] *Id.* at *5 and Table 2 (indicated by lack of an asterisks next to the P column for the Univariate Analyses). See also use of the asterisks in Table 1, at *4.
[241] See generally M. Biggs, Comment on J. L. Turban, Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation, 145 Pediatrics e20191725, Comment published on Jan. 30, 2020, available at https://publications.aap.org/pediatrics/article/145/2/e20191725/68259/Pubertal-Suppression-for-Transgender-Youth-and?autologincheck=redirected (last visited April 24, 2023), and the multiple Letters to the Editor that criticized the multiple methodological errors in this study, https://pediatrics.aappublications.org/content/145/2/e20191725/tab-e-letters#re-pubertal-suppression-for-transgender-youth-and-risk-of-suicidal-ideation. See also M. Biggs, Puberty Blockers and Suicidality in Adolescents Suffering from Gender Dysphoria, 49 Archs. Sex. Behav. 2227 (2020).

Thus, much like the previously discussed Turban et al. 2019-2020 JAMA Psychiatry study, this Turban et al. 2020 Pediatrics study is severely compromised by unsound methodology, flawed and biased data from the 2015 USTS, and improper or weak extrapolations.

A 2020 study by Van der Miesen et al.[242] was a cross-sectional Dutch study that measured some patients who received puberty blockers and some who did not. The study had three populations of subjects: One was patients presenting to the gender clinic who had not received any intervention, the second was patients who had received puberty blocker, and the third was adolescents from the general population.[243] Because of this study's cross-sectional nature, it cannot establish a causal relationship between intervention and effect. It also represents a non-probability sample with potential for significant biases in subject recruitment. In addition, the subjects assessed before and after treatment are different populations. Among the differences between these groups is patient age (mean of 14.5 and 16.8 years before and after treatment, respectively).[244] This two-year age difference is important as developmental progress during adolescence is known to influence psychological well-being.[245] There was also the same limitation noted in the 2011 de Vries study, that the treated population also received psychological support.[246]

A 2021 study by Bustos et al.[247] attempts to provide a systematic review of 27 observational or interventional studies that report on regret or detransition following gender-transition

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[242] A. I. R. van der Miesen et al., Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers, 66 J. Adolesc. Health 699 (2020).
[243] *Id.* at 700.
[244] *Id.*
[245] J. He et al., Meta-analysis of gender differences in body appreciation, 33 Body Image 90 (2020).
[246] A. I. R. van der Miesen et al. (2020), Psychological Functioning, 66 J. Adolesc. Health, at 703.
[247] V. P. Bustos et al., Regret after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence, 9 Plastic and Reconstructive Surg. - Global Open e3477 (2021); Regret

surgeries. A total of 7,928 subjects were included in their meta-analysis.[248] The authors concluded that only 1% or less of those who had gender-transition surgeries expressed regret.[249] It is important to understand the serious methodological limitations and high risk of bias contained within this study's analysis.[250] This includes failure to include major relevant studies addressing this question,[251] inaccurate analysis within one of the studies considered,[252] and the general lack of controlled studies, incomplete and generally short-term follow-up, large numbers of lost subjects, and lack of valid assessment measures in the published literature addressing this question.[253] As noted by Expósito-Campos and D'Angelo (2021), moderate to high risk of bias was present in 23 of the 27 studies included in the analysis.[254] Furthermore, 97% of subjects analyzed were found within studies deemed to be of fair to poor scientific quality.[255] Thus, this study cannot be used as strong support for the contention that regret is rare.

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after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence—Erratum, 10 Plastic and Reconstructive Surg. – Global Open e4340 (2022) ("The systematic review was re-conducted, and the meta-analysis was re-run with the updated numbers with no significant or major changes. The updated tables and figures are included below.").0

[248] V. P. Bustos et al. (2021), Regret after Gender-affirmation Surgery, 9 Plastic and Reconstructive Surg. – Global Open e3477, at *1.

[249] *Id.*

[250] See P. Expósito-Campos et al., Letter to the Editor: Regret after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence, 9 Plastic and Reconstructive Surg. - Global Open e3951 (2021).

[251] *Id.* See, e.g., C. Dhejne et al., An Analysis of All Applications for Sex Reassignment Surgery in Sweden, 1960-2010: Prevalence, Incidence, and Regrets, 43 Archs. Sex. Behav. 1535 (2014).

[252] C. M. Wiepjes et al., The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets, 15 J. Sexual Med. 582 (2018).

[253] P. Expósito-Campos et al. (2021), Letter to the Editor regarding Bustos et al., Regret after Gender-affirmation Surgery, (2021), 9 Plastic and Reconstructive Surg., at *1.

[254] *Id.*

[255] *Id.*

The 2021 study by Narayan et al.[256] examines anonymous survey results from 154 surgeons affiliated with WPATH. The response rate for this survey was 30%.[257] Of the respondents, 57% had encountered patients with surgical regret.[258] It is important to recognize that this study was specifically directed toward patients who had undergone surgical transition. Acknowledged biases of this study include selection bias, recall bias, and response bias.[259] This type of study cannot accurately identify the prevalence in the transgender population as a whole, and is particularly limited in the ability to assess potential for regret in the pediatric population.

The 2021 Almazan et al. study is "a secondary analysis of data from the 2015 US Transgender Survey" (USTS).[260] As a secondary analysis that is entirely reliant on the highly flawed and bias 2015 USTS data set, this study is subject to the resulting deficiencies already discussed above in the summaries of the 2019-2020 Turban et al. JAMA Psychiatry study and the 2020 Turban et al. Pediatrics study.

In addition, the Almazan study itself has come under even more direct critique. In a Comment in response to the study, D. Curtis noted that the two groups the study compared are too dissimilar to one another to draw meaningful conclusions and that the authors failed to adequately highlight the magnitude of several differences.[261] Curtis lists a number of these differences —

[256] S. K. Narayan et al., Guiding the conversation—types of regret after gender-affirming surgery and their associated etiologies, 9 Annals of Translational Med. 605 (2021).
[257] *Id.*
[258] *Id.*
[259] *Id.* at 9.
[260] A. N. Almazan et al., Association Between Gender-Affirming Surgeries and Mental Health Outcomes, 156 JAMA Surg. 611 (2021).
[261] D. Curtis, Unrecognized confounding may explain differences in mental health outcomes, Comment on A. N. Almazan et al., Association Between Gender-Affirming Surgeries and Mental Health Outcomes, 156 JAMA Surg. 611 (2021), available at https://jamanetwork.com/journals/jamasurgery/fullarticle/2779429.

including significant differences in age, education (degree-status), employment status, gender identification, household income, and sexual orientation. — and then concludes:

> The two groups are so radically different that we really cannot assume that the multivariate analyses carried out allow us to conclude that differences in psychopathology are likely the result of surgical intervention. . . . We cannot agree that the results provide strong evidence that gender-affirming surgery is causally associated with improved mental health outcomes.[262]

In short, the Almazan study is discredited by both unreliable data and improper comparisons.

The 2022 Van der Loos study[263] is a Dutch cohort study that investigates the continuation rate of gender affirming interventions in people who began puberty blockers and gender affirming hormones during adolescence. The authors claim that the study provides evidence against desistance after receiving gender-affirming hormones. While the paper gives the impression that subjects represent a period of study extending from 1972 to 2018, the majority of subjects recently started hormone interventions. The length of time for follow-up (mean of 3.5 years for males and 2.3 years for females) and the average age at follow-up (20.2 years for males and 19.3 years for females) are inadequate to support the authors' claim. Notably, research from these same investigators has suggested that the average time to detransition is over 10 years.[264] Thus, it would be necessary for the study to assess patients at least a decade after starting gender-affirming hormones to make any meaningful conclusions on desistance. Furthermore, as a retrospective cohort study without a control group, the study design cannot determine the effect of gender affirming therapy

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[262] *Id.*

[263] M. A. T. C. van der Loos et al. (2022), Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence, 6 Lancet Child & Adolesc. Health at 869-75.

[264] C. M. Wiepjes et al. (2018), The Amsterdam Cohort of Gender Dysphoria Study (1972-2015), 15 J. Sexual Med., at 582-90.

on whether the intervention influences the rate of desistance that would have occurred without the provision of gender-affirming hormones.

The 2022 Nos et al. study[265] is a retrospective cohort study that reports on the likelihood of starting on gender-affirming hormones (GAH) based upon whether or not subjects were treated with puberty blockers. While the title and abstract give the impression that puberty blocker use is not linked to subsequent GAH, the data fail to support this conclusion. Since nearly all of the patients in this study who did not receive GnRHa were given GAH, it is not possible to determine whether GnRHa could increase this outcome. The comparison groups differed by age at time of initial presentation (age 10-13 years versus 14-17 years). GnRHa use was higher among the younger patients owing to the fact that they had not completed puberty at the time of first visit. A lag in progression to GAH use in this group is heavily influenced by the difference in age at time of initial presentation. The older group was eligible to start GAH at the time of study entry while those in the younger group were not. When adjusted for age, the rates of progression to GAH use is nearly identical. Importantly, among the patients who received GnRHa, 94% (64 out of 70) went on to take gender affirming hormones. Thus, the study further confirms that, rather than serving as a "pause button" for gender dysphoric adolescents, GnRHa use is an intervention that will lead to progression to gender affirming hormones.

[265] A. L. Nos et al., Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents, 5 JAMA Netw. Open e2239758 (2022).

The 2022 Green at al. study[266] purported to measure suicide attempts and access to cross-sex hormones. Though this study had a large cohort of patients,[267] it suffered many biases in patient recruitment — which was done over the Internet[268] and provided a cross-sectional analysis[269] which can, at best, demonstrate correlation but not causation. Similar to other studies, it did not assess the effect of psychiatric medications or psychotherapy on outcomes. It also failed to include variables to assess at what age youth began puberty blockers or the duration which they had received gender-affirming hormones.

The 2022 Turban et al. study[270] is a retrospective cross-sectional investigation to assess whether there is an association between adolescent access to gender-affirming hormones and mental health. By nature of its retrospective cross-sectional design, the study is not able to make any conclusions regarding a causal relationship between GAH access and mental health. Like the Almazan et al. study and the two prior studies from Turban discussed above, this 2022 Turban study rests entirely on data from the USTS[271] and therefore suffers from similar defects.[272] Caution is warranted in evaluating any and all studies that either use or conduct further analysis of the USTS data because those studies would naturally be subject to any limitations, flaws, biases, irregularities, or anomalies in this source data.

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[266] A. E. Green et al., Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth, 70 J. Adolesc. Health 643 (2022).
[267] *Id.* at 644.
[268] *Id.*
[269] *Id.* at 647.
[270] J. L. Turban et al., Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults, 17 PLOS ONE e0261039 (2022).
[271] *Id.* at *3.
[272] See supra discussion of Alamazan et al., USTS, D'Angelo et al, and D. Curtis comment on Almazan et al.

The authors of the Turban 2022 study claim that there is an association between getting gender-affirming hormones and favorable mental health outcomes compared to those who desired but did not receive this intervention.[273] However, since the methodology used is similar to the author's 2020 study on the effects of access to puberty blockers on lifetime suicidality, already discussed above, and used the same 2015 U.S. Transgender Survey (USTS), it is subject to all of the associated limitations and biases.[274] Participants in the USTS were recruited through transgender advocacy organizations and subjects were asked to "pledge" to promote the survey among friends and family.[275] Thus, there are serious concerns of selection bias.[276] It also suffers from recall bias[277] and an inability to verify the veracity of the claims of treatments given to the study respondents.

Review of the data contained within the paper leads to conclusions that are far different than those stated by the study authors regarding mental health of the study participants. While the odds ratio for past-year suicidal ideation was statistically different between those who did and those who did not get GAH, there was no difference in those who had a suicide plan, actually attempted suicide, or were hospitalized for a suicide attempt.[278] This is important since the rationale for accepting the attendant risks of gender-affirming hormones is to prevent suicide. As

[273] J. L. Turban et al. (2022), Access to gender-affirming hormones, 17 PLOS ONE e0261039, at *1, *1.
[274] D'Angelo et al. (2021), One Size Does Not Fit All, 50 Archs. Sex. Behav. at 7-16.
[275] *Id.* at 8.
[276] S. Tyrer et al., Sampling in epidemiological research: issues, hazards and pitfalls, 40 BJPsych Bull. 57 (2016).
[277] See generally S. S. Coughlin, Recall bias in epidemiologic studies, 43 J. Clin. Epidemiol. 87 (1990).
[278] J. L. Turban et al. (2022), Access to gender-affirming hormones, 17 PLOS ONE e0261039, at *5-*8 ("We detected no difference for other mental health variables measured.").

pointed out by Michael Biggs in a commentary on this article,[279] the data presented in this study negate the purported significance of effects of puberty blocker access on mental health as reported in Turban's 2020 Pediatrics article. As with many of the other studies considered in this report, the Turban et al. 2022 study is also discredited both by deficient data-sampling techniques and by flawed reasoning and unsound methodology overall.

The 2022 Tordoff study[280] is a prospective observational cohort study that assessed the mental health of patients presenting to the Seattle Children's gender clinic over a one-year period of follow-up. The authors claimed that access to gender-affirming care had significantly improved mental health with lower odds ratios of depression and suicidality. This purported finding was widely publicized by the University of Washington and was featured on several news media sites.[281] A detailed critique of the paper's data and flawed conclusions has been posted online.[282]

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[279] M. Biggs, Estrogen is associated with greater suicidality among transgender males, and puberty suppression is not associated with better mental health outcomes for either sex, Comment on J. L. Turban et al., Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults, 17 PLOS ONE e0261039 (2022), Comment posted on Jan. 19, 2022, available at https://journals.plos.org/plosone/article/comment?id=10.1371/annotation/dcc6a58e-592a-49d4-9b65-ff65df2aa8f6 ("Conversely, a previous article by Turban et al. claimed to find a positive association between puberty suppression (using a Gonadotropin-Releasing Hormone agonist) and mental health--but this did not control for cross-sex hormones." (citing J. L. Turban et al. 2020, Pubertal suppression, 145 Pediatrics e20191725)).

[280] D. M. Tordoff et al., Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care, 5 JAMA Netw. Open e220978 (2022). For errata, see Data Errors in eTables 2 and 3, 5 JAMA Netw. Open e2229031 (2022).

[281] See, e.g., Teens who received gender-affirming care had 60% lower odds of depression, UW study finds, king5.com, Published Mar. 12, 2022, Updated Sept. 7, 2022, https://www.king5.com/article/news/health/gender-affirming-care-reduces-depression-university-of-washington-study-transgender-nonbinary/281-bcfece1b-a7cb-4c95-80d0-3f02c597d783 (last visited Apr 30, 2023); Medical treatments cut risks for depression, suicide among transgender youth, UPI, https://www.upi.com/Health_News/2022/03/01/medical-treatments-transgender-youth/3211646078081/ (last visited Apr 30, 2023).

[282] See J. Singal, Researchers Found Puberty Blockers And Hormones Didn't Improve Trans Kids' Mental Health At Their Clinic. Then They Published A Study Claiming The Opposite. (Up-

Contrary to the authors' claims, data contained in the paper did not show improvement in mental health over the one-year study period. At entry into the study, 57% of the subjects who reported receiving treatment with puberty blockers or gender-affirming hormones (PB/GAH) had moderate to severe depression.[283] At the end of the study, 56% of the subjects who reported receiving PB/GAH had moderate to severe depression.[284] Rates for moderate to severe anxiety were 57% and 51% at baseline and 12 months, respectively, for subjects who reported receiving PB/GAH.[285] Self-harm or suicidal thoughts were 43% and 37% at baseline and 12 months, respectively for subjects who reported receiving PB/GAH.[286] These are alarmingly high numbers for an intervention that is touted to be lifesaving. J. Singal notes that "[a]mong the kids who went on hormones, there isn't genuine statistical improvement here from baseline to the final wave of data collection.[287] Singal contacted one of the authors to ask about the data in eTable 3 and to confirm that there was, in fact, no improvement within the group of participants that had received puberty-blocking or hormonal interventions. Singal writes:

> [The authors] reference "improvements" twice . . . but offer no statistical demonstration anywhere in the paper or the supplemental material. I wanted to double-check this to be sure, so I reached out to one of the study authors. They wanted to stay on background, but they confirmed to me that there was no improvement over time among the kids who went on hormones or blockers.[288]

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dated), Singal-Minded (Apr. 6, 2022), https://jessesingal.substack.com/p/researchers-found-puberty-blockers (last visited Apr 13, 2023). See also Jesse Singal, Authors, Macmillan, https://us.macmillan.com/author/jessesingal (last visited Apr 30, 2023).

[283] D. M. Tordoff et al. (2022), Mental Health Outcomes, 5 JAMA Netw. Open e220978, at Online Supplementary Materials (Tordoff Supplement) and eTable 3 (at *4).

[284] *Id.*

[285] *Id.*

[286] *Id.*

[287] J. Singal (2022), Research Found Puberty Blockers And Hormones Didn't Improve Trans Kids' Mental Health, https://jessesingal.substack.com/p/researchers-found-puberty-blockers (last visited Apr 30, 2023).

[288] J. Singal (2022), Research Found Puberty Blockers And Hormones Didn't Improve Trans Kids' Mental Health, https://jessesingal.substack.com/p/researchers-found-puberty-blockers (last visited

The reported statistical difference in odds ratios were comparisons between those who started on puberty blockers and cross-sex hormones and those who did not receive hormones. Importantly, there was a marked difference in the number of dropout subjects in the treated and non-treated groups (17.4% versus 80%, respectively).[289] It is reasonable to speculate that the small number of subjects who remained in the study but did not receive hormones had significant co-morbidities that prevented them from accessing this intervention. In any event, the actual data from this study demonstrates that access to puberty blockers and gender affirming hormones did not improve mental health over the first year of treatment. This is drastically different from what the authors and the media claimed.

The 2023 Chen et al. study[290] is a longitudinal observational study of patients receiving care at four gender centers in the United States. The primary conclusion made by the authors is that "GAH improved appearance congruence and psychosocial functioning."[291] However, there are major limitations and weaknesses in the data that limit the conclusions that can be made. The most glaring problem is that the study was observational and did not include a control group. Thus, there is no ability to draw causal conclusions. At best, the authors can find associations. A revealing critique of the paper by De Vries and Hannema that was published alongside this article

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Apr 30, 2023) (linking at the phrase "on background" to J. Bender et al., Levels of Attribution, in J. Bender et al., Writing & Reporting for the Media, 11th ed., Oxford University Press (2016), available at https://global.oup.com/us/companion.websites/9780190200886/student/chapter10/gline/level/#:~:text=%E2%80%9COn%20background%2C%E2%80%9D%20which%20is,the%20source%20by%20her%20position. (last visited May 1, 2023)).

[289] D. M. Tordoff et al. (2022), Mental Health Outcomes, 5 JAMA Netw. Open e220978, at 1, and Tordoff Supplement at eTable2 (*4), eTable3 (*4). See also J. Singal (2022), Research Found Puberty Blockers And Hormones Didn't Improve Trans Kids' Mental Health, at nn.3-4.

[290] D. Chen et al., Psychosocial Functioning in Transgender Youth after 2 Years of Hormones, 388 N. Engl. J. Med. 240 (2023).

[291] *Id.* at 240.

exposes some of these concerns.[292] Akin to many of the other papers in this field, there is no way to determine whether any of the changes were contributed by or due solely to psychiatric interventions.[293] It is also notable that even though the study was designed to recruit only subjects with good mental health at baseline, 48 of the 307[294] study subjects (15.6%) were described as having severe or moderate depression at this time point.[295] At the end of the two-year follow-up, 30 of the 219 remaining subjects (13.7%) were reported to have major depression. Furthermore, two patients committed suicide during the two-year observation period, "one after 6 months of follow-up and the other after 12 months of follow-up."[296] This is an outcome that in most other situations would lead to a halt in study and detailed inquiry by an institutional review board.[297] The paper claims to present two-year follow-up data in this cohort. However, only about half of the study participants were assessed at all five of the study time points,[298] and 30% did not have 24-month data collected.[299] Even if one accepted the follow-up period, this is likely not long enough to make

[292] A. L. C. De Vries et al., Growing Evidence and Remaining Questions in Adolescent Transgender Care, 388 N. Engl. J. Med. 275, (2023).
[293] *Id.* at 276.
[294] While 315 participants enrolled in the Chen study, only 307 participants remained at the conclusion of the study. D. Chen et al. (2023), Psychosocial Functioning, 388 N. Engl. J. Med. at 243.
[295] *Id.* at 243.
[296] *Id.* at 243.
[297] NIH Guide: Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials, NOT-99-107, June 11, 1999, available at https://grants.nih.gov/grants/guide/notice-files/NOT99-107.html (last visited Apr 13, 2023) (also accessible through NIH Funding Opportunities and Notices for The Week Ending 06-11-99, available at https://grants.nih.gov/grants/guide/WeeklyIndex.cfm?WeekEnding=06-11-99 (last visited Apr 13, 2023)). See also NIH Grant Policy Statement, § 4.1.15.6 Data and Safety Monitoring (U.S. Department of Health and Human Services, National Institutes of Health, December 2022) available at https://grants.nih.gov/grants/policy/nihgps/nihgps.pdf (last visited April 13, 2022) (setting planning standards for reporting of adverse events to institutional review boards in NIH grant-funded clinical trials).
[298] D. Chen et al. (2023), Psychosocial Functioning, 388 N. Engl. J. Med. at 240.
[299] D. Chen et al. (2023), Psychosocial Functioning, 388 N. Engl. J. Med. at 240, Supplementary Appendix at 8 (Table S2. Coverage for Key Variables).

firm conclusions about long-term efficacy. Several key outcomes that according to the original study protocol were to be measured (gender dysphoria, trauma symptoms, self-injury, suicidality, body esteem, and quality of life) are not reported in this paper.[300] The reason for these omissions is not apparent in the published manuscript. The study authors failed to report on robust measures of psychological well-being such as the number on antidepressants and other psychotropic medications.[301] The study effects for many of the measures reported was very modest at best and, even when statistically significant, do not have any meaningful clinical significance. For example, the depression scores showed little change over two years in the highest severity group.[302] There is also significant heterogeneity in responses with some subjects showing improvement, some no change, and others worsening.[303] Consequently, these data do not alleviate the serious concerns raised regarding the safety and efficacy of gender-affirming medical interventions.

129. Many conclusions in the above studies are drawn or characterized in fundamentally unscientific ways without apparent regard to the scientific process of disproving a null hypothesis. Instead, these studies — along with the comments, responses, and professional criticism they have received — suggest that the authors began with a conclusion and then looked for data to support that conclusion. That is a vastly unsound way of doing science, and patients will not be aware of these methodological limitations and distortions when informed of these purported conclusions.

[300] D. Chen et al. (2023), Psychosocial Functioning, 388 N. Engl. J. Med. at 240-50.
[301] *Id.*
[302] D. Chen et al. (2023), Psychosocial Functioning, 388 N. Engl. J. Med. at 240, Supplementary Appendix at 13 (Table S6. Proportions of Youth Scoring in the Clinical Range for Depression and Anxiety at Each Timepoint).
[303] D. Chen et al. (2023), Psychosocial Functioning, 388 N. Engl. J. Med. at 240-50.

130. There remains a significant and unmet need to improve our understanding of the biological, psychological, and environmental basis for the manifestation of patient reports of discordance of gender identity and biological sex in affected individuals, as well as the long-term effects of "affirming" interventions.[304] In particular, there is a concerning lack of randomized controlled trials or adequately controlled longitudinal studies comparing outcomes of youth with gender dysphoria who received psychological support, were encouraged to socially transition, or were put on medical interventions, and how these differential treatments affect the usual and natural progression to resolution of gender dysphoria and other variables. Such studies can be ethically designed and executed with provisions for other dignity-affirming measures to all treatment groups.[305] But they have not been performed in the existing literature, leaving that literature in a state insufficient to enable sound conclusions about the efficacy of "affirming" treatments.

INTERNATIONAL RESPONSES

131. Recognizing the paucity of evidence supporting "affirming" treatments, along with the proven risks of those treatments, other countries are increasingly limiting use of those treatments.

132. **Finland**: The National Science Review in Finland carefully examined all relevant science and suspended transition treatments for minors under age 16.[306] The review determined

[304] J. Olson-Kennedy et al., Research priorities for gender nonconforming/transgender youth: gender identity development and biopsychosocial outcomes, 23 Current Op. in Endocrinol., Diabetes & Obesity 172, 172-79 (2016).
[305] See generally J. Sugarman, Ethics in the Design and Conduct of Clinical Trials, 24 Epidemiologic Reviews 54, 54-58 (2002).
[306] See 2020 Recommendation of the Council for Choices in Health Care in Finland (PALKO / COHERE Finland) Medical Treatment Methods for Dysphoria Related to Gender Variance in Minors, Palveluvalikoima, Nov. 6, 2020, available at https://segm.org/sites/default/files/Finnish_Guidelines_2020_Minors_Unofficial%20Translation.pdf. See also Recommendations -

that "[t]he first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and treatment of possible comorbid psychiatric disorders."[307] According to the review, "[c]ross-sex identification in childhood, even in extreme cases, generally disappears during puberty."[308] The review also found: "Potential risks of GnRH therapy include disruption in bone mineralization and the as yet unknown effects on the central nervous system";[309] "there are no medical treatment[s] [for transitioning] that can be considered evidence-based";[310] and, "[t]he reliability of the existing studies with no control groups is highly uncertain."[311] Thus, "because of this uncertainty, no decisions should be made that can permanently alter a still-maturing minor's mental and physical development,"[312] and "[n]o gender confirmation surgeries are performed on minors."[313] "Since reduction of psychiatric symptoms cannot be achieved with hormonal and surgical interventions, it is not a valid justification for gender reassignment. A young person's identity and personality development must be stable so that they can genuinely face and discuss their gender dysphoria, the significance of their own feelings, and the need for various treatment options. For children and adolescents, these factors are key reasons for postponing any interventions until adulthood. . . . In light of available evidence, gender reassignment of minors is an experimental practice."[314]

Choices in health care, Palveluvalikoimaneuvosto, https://palveluvalikoima.fi/en/recommendations (last visited Apr 13, 2023).

[307] PALKO / COHERE Finland, Recommendation, Nov. 6, 2020 (unofficial translation), at 5.

[308] *Id.*

[309] *Id.* at 6.

[310] *Id.*

[311] *Id.* at 7.

[312] *Id.*

[313] *Id.*

[314] *Id.* at 7-8.

133. **Sweden**: The world-renowned Karolinska Hospital reviewed the current research and suspended pediatric gender transitions for patients under 16 outside of experimental, monitored clinical trials settings as of May 2021.[315] Treatment will focus on psychotherapy and assessment.[316] The "Dutch protocol" for treating gender-dysphoric minors has been discontinued over concerns of medical harm and uncertain benefits.[317]

Moreover, in a national policy review, a report commissioned by the Swedish government concluded that:

- We have not found any scientific studies which explains the increase in incidence in children and adolescents who seek the heath care because of gender dysphoria.

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[315] Karolinska Universitetssjukhuset — Astrid Lindgrens Barnsjukhus, English, unofficial translation, Guideline Regarding Hormonal Treatment of Minors with Gender Dysphoria at Tema Barn - Astrid Lindgren Children's Hospital (ALB), K2021-4144, Apr. 2021, at 2, available at https://segm.org/sites/default/files/Karolinska%20Guideline%20K2021-4144%20April%202021%20%28English%2C%20unofficial%20translation%29.pdf; Karolinska Universitetssjukhuset — Astrid Lindgrens Barnsjukhus, English, unofficial translation, Policy Change Regarding Hormonal Treatment of Minors with Gender Dysphoria at Tema Barn - Astrid Lindgren Children's Hospital, K2021-3343, Mar. 2021, at 1-2, available at https://segm.org/sites/default/files/Karolinska%20Policy%20Change%20K2021-3343%20March%202021%20%28English%2C%20unofficial%20translation%29.pdf. See also Karolinska Universitetssjukhuset — Astrid Lindgrens Barnsjukhus, Riktlinje gällande hormonell behandling till minderariga patienter med könsdysfori inom Tema Barn, K2021-4144, Apr. 2021, available at https://segm.org/sites/default/files/Karolinska%20Riktlinje%20K2021-4144%20April%202021%20%28Swedish%29.pdf (Swedish-language document); Karolinska Universitetssjukhuset — Astrid Lindgrens Barnsjukhus, Policyförändring gällande hormonell behandling till minderariga patienter med könsdysfori inom Tema Barn - Astrid Lindgrens Barnsjukhus, K2021-3343, Mar. 2021, available at https://segm.org/sites/default/files/Karolinska%20Policyförändring%20K2021-3343%20March%202021%20%28Swedish%29.pdf (Swedish-language document).

[316] See Society for Evidence-Based Medicine, Sweden's Karolinska Ends All Use of Puberty Blockers and Cross-Sex Hormones for Minors Outside of Clinical Studies, SEGM.org, May 5, 2021, https://segm.org/Sweden_ends_use_of_Dutch_protocol ((featuring links to PDF copies of the Karolinska Policy and Guidelines documents, along with unofficial English translations, at the bottom of the page).

[317] *Id.*

- We have not found any studies on changes in prevalence of gender dysphoria over calendar time, nor any studies on factors that can affect the societal acceptance of seeking for gender dysphoria.

- There are few studies on gender affirming surgery in general in children and adolescents and only single studies on gender affirming genital surgery.

- Studies on long-term effects of gender affirming treatment in children and adolescents are few, especially for the groups that have appeared during the recent decennium. . . .

- . . . No relevant randomized controlled trials in children and adolescents were found.[318]

From these findings, the Swedish National Board of Heath in December of 2022 issued updated guidelines for the care of adolescents and children with gender dysphoria.[319] This medical board concluded that "the risks of puberty blockers and gender-affirming treatment are likely to outweigh the expected benefits of these treatments."[320] Noting that there is uncertainty about the cause for the rapid rise in number of people being diagnosed with gender dysphoria, documented

[318] See Sweden Policy Review, Gender dysphoria in children and adolescents: an inventory of the literature, SBU Policy Support no 307, 2019, https://www.sbu.se/307e.

[319] Socialstyrelsen —The National Board of Health and Welfare, Vård av barn och ungdomar med könsdysfori Nationellt kunskapsstöd med rekommendationer till profession och beslutsfattare (2022), https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302.pdf (full report in Swedish, PDF format). See also Uppdaterat kunskapsstöd för vård vid könsdysfori hos unga, Socialstyrelsen (2022), https://www.socialstyrelsen.se/om-socialstyrelsen/pressrum/press/uppdaterat-kunskapsstod-for-vard-vid-konsdysfori-hos-unga/ (last visited Apr 14, 2023) (announcing and publishing the full Swedish report); Socialstyrelsen —The National Board of Health and Welfare, Care of children and adolescents with gender dysphoria Summary of national guidelines, December 2022, https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2023-1-8330.pdf (English-language Summary from Socialstyrelsen).

[320] Socialstyrelsen —The National Board of Health and Welfare, Care of children and adolescents with gender dysphoria Summary of national guidelines, December 2022, at 3, https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2023-1-8330.pdf (English-language Summary from Socialstyrelsen). See also J. Block (2023), Gender dysphoria in young people is rising-and so is professional disagreement, 380 BMJ 382, at *2, *3.

evidence of detransitioning young adults with uncertainty regarding the prevalence of this outcome, and lack of uniformity in experience-based knowledge among providers, GnRH analogues, gender-affirming hormones and mastectomy should be provided only in exceptional cases and ideally as part of an experimental trial.[321]

The results of the Swedish systematic review of the current published literature related to hormone treatment of gender dysphoric youth that served as the basis for this policy change were pubished on April 17, 2023 in the peer reviewed journal Acta Paediatrica.[322] The authors of this systematic review identified 9,934 abstracts related to hormone administration to childen with gender dysphoria among the English language literature as of November 9, 2022. From these abstracts, 36 studies met their rigorous inclusion criteria for in-depth analysis. Twelve studies were assessed to have a high risk of bias and were therefore excluded from analysis. The remaining 24 studes were assessed for findings relevant to the inclusion criteria. This included 21 studies in which adolescents were given GnRH analogues (a.k.a. puberty blockers) and 3 studies where cross-sex hormones were administered without prior GnRHa treatment. Among the studies, the authors did not find any randomized controlled trials addressing the psychosocial effects, bone health, body composition and metabolism or persistence in children with gender dyshporia undergoing treatment with GnRHa medications. The authors of this study found serious methodological weaknesses in each of the the three longitudinal observational studies assessed. This included small sample size, and high attrition rates. This prevented any verifiable conclusions regarding the long-term effects of hormone therapy on psychological health to be drawn. GnRHa

[321] *Id.* at 3-4.
[322] Ludvigsson JF, Adolfsson J, Höistad M, Rydelius PA, Kriström B, Landén M. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. Acta Paediatr. 2023 Apr 17. doi: 10.1111/apa.16791. Epub ahead of print. PMID: 37069492.

therapy was found to delay bone maturation and bone mineral density gain that was only partially recovered by cross-sex hormone administration when studied at age 22 years. Among the key finding of this published peer reviewed study were that the long long-term effects of hormone therapy on psychosocial health are unknown, GnRHa treatment delays bone maturation and gain in bone mineral density and that GnRHa treatment in children with gender dysphoria should be considered experimental treatment of individual cases rather than standard procedure.

134. **United Kingdom**: The British official medical review office, National Institute of Health and Care Excellence (NICE), published reports on the use of both puberty blockers and hormones for transitioning purposes.[323] The assessment of the evidence into the drugs was commissioned by the National Health Service England (NHS). The review found that the evidence for using puberty-blocking drugs to treat young people struggling with their gender identity is "very low certainty."[324] The review on GnRH analogues found only "small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are of very low certainty using modified GRADE. They all reported physical and mental health comorbidities and concomitant treatments very poorly."[325]

[323] Nice Evidence Reviews — Cass Review, https://cass.independent-review.uk/nice-evidence-reviews/ (last visited Apr. 29, 2023).
[324] NICE, Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria, (Oct. 2020), https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_GnRH-analogues_For-upload_Final.pdf.
[325] *Id.* at 11-12.

NICE also reviewed the evidence base for cross-sex hormones.[326] This review found the evidence of clinical effectiveness and safety of cross-sex hormones was also of "very low" quality.[327] The review concluded: "Any potential benefits of gender-affirming hormones must be weighed against the largely unknown long-term safety profile of these treatments in children and adolescents with gender dysphoria."[328]

A recent independent review of gender identity services in the United Kingdom, by Dr. Hilary Cass, concluded that "Evidence on the appropriate management of children and young people with gender incongruence and dysphoria is inconclusive both nationally and internationally."[329] In summarizing a few of the key points and context from the Interim Report, the Cass Review stated, "There is lack of consensus and open discussion about the nature of gender dysphoria and therefore about the appropriate clinical response."[330]

Following the Cass Review, the NHS ordered the closure of the Tavistock clinic, the UK's only dedicated gender identity clinic for children and young people.[331] As the BBC summarized, the Cass Review found that "the current model of care was leaving young people 'at considerable risk' of poor mental health and distress, and having one clinic was not 'a safe or viable long-term option.'"[332] The Tavistock will be replaced by a new regional hospital-based

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[326] NICE, Evidence review: Gender-affirming hormones for children and adolescents with gender dysphoria, (Oct. 2020), https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_Gender-affirming-hormones_For-upload_Final.pdf.
[327] See, e.g., *id.* at 7, 47.
[328] *Id.* at 14.
[329] H. Cass (2022), The Cass Review — Interim Report, at 18.
[330] The Cass Review, Interim report — Cass Review, Publications, https://cass.independent-review.uk/publications/interim-report/ (last visited Apr 14, 2023) (announcing the submission of the Interim Report to NHS and summarizing some key findings).
[331] J. Andersson et al., NHS to close Tavistock child gender identity clinic, BBC News, Jul. 28, 2022, https://www.bbc.com/news/uk-62335665.
[332] *Id.*

service where related services for mental health and autism can be provided by clinicians who have expertise in safeguarding and supporting children.[333] Thus, gender-related distress will be addressed "within a broader child and adolescent health context."[334]

This new model is in sharp contrast to recommendations made by WPATH in SOC-8. (Indeed, WPATH criticizes the UK's recent approach.[335]) Differences in approach include the prioritization of parent versus child expectations for care, recommendations against social affirmation of pre-pubertal youth, the provision of puberty blockers within the experimental setting, initial focus on exploration and treatment of mental health problems, and use of psychological support as a primary intervention.[336]

135. **Norway:** Adding to the growing list of European countries acknowledging the lack of reliable scientific evidence supporting the gender affirmation model, the Norwegian Healthcare Investigation Board (Ukom) issued in March of 2023 a new report on the treatment of people with gender incongruence and gender dysphoria.[337]

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[333] Letter from Dr. Hilary Cass, Chair, Independent Review of Gender Identity Services for Children and Young People, to John Stewart, National Director Specialised Commissioning, NHS England, (Jul. 19, 2022), at 2, https://cass.independent-review.uk/wp-content/uploads/2022/07/Cass-Review-Letter-to-NHSE_19-July-2022.pdf.

[334] *Id.*

[335] WPATH, WPATH, ASIAPATH, EPATH, PATHA, and USPATH Response to NHS England in the United Kingdom (UK) Statement regarding the Interim Service Specification for the Specialist Service for Children and Young People with Gender Dysphoria (Phase 1 Providers) by NHS England, (2022), https://www.wpath.org/media/cms/Documents/Public%20Policies/2022/25.11.22%20AUSPATH%20Statement%20reworked%20for%20WPATH%20Final%20ASIAPATH.EPATH.PATHA.USPATH.pdf?_t=1669428978#:~:text=the%20specialist%20service.-,WPATH%2C%20ASIAPATH%2C%20EPATH%2C%20PATHA%2C%20and%20USPATH%20believe%20that,to%20puberty%20suppression%20and%20gender%2D.

[336] See generally, E. Coleman et al. (2022), SOC-8, 23 Int'l. J. Transgender Health, at 51-5258; H. Cass (2022), The Cass Review – Interim Report.

[337] Ukom. Pasientsikkerhet for barn ogunge med kjønnsinkongruens. https://ukom.no/rapporter/pasientsikkerhet-for-barn-og-unge-med-kjonnsinkongruens/sammendrag March 2023

As reported by Jennifer Block in the BMJ,[338] this report is highly critical of the guidelines published by Norway's Healthcare directory in 2020. The report expressed concerns that the 2020 guidelines were not based upon systematic review of the scientific literature on the treatment of gender dysphoria. According to Stine Marit Moen, Ukom's medical director, "The report found that there is insufficient evidence for the use of puberty blockers and cross sex hormone treatments in young people, especially for teenagers who are increasingly seeking health services and being referred to specialist healthcare. Ukom defines such treatments as utprøvende behandling, or 'treatments under trial.'"[339]

CONCLUSIONS

136. There are no long-term, peer-reviewed, published, reliable, and valid research studies documenting the reliability and validity of assessing gender identity by relying solely upon the expressed desires of a patient.

137. There are no long-term, peer-reviewed, published, reliable, and valid research studies documenting any valid and reliable biological, medical, surgical, radiological, psychological, or other objective assessment of gender identity or gender dysphoria.

138. A large percentage of children (over 80% in some studies) who questioned their gender identity will, if not affirmed in a sex-discordant gender identity, develop an acceptance of their natal (biological) sex.

139. A currently unknown percentage and number of patients reporting gender dysphoria suffer from mental illness(es) that complicate and may distort their judgments and perceptions of gender identity.

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[338] Block J. Norway's guidance on paediatric gender treatment is unsafe, says review. BMJ. 2023 Mar 23;380:697

[339] *Id*

140. There are no long-term, peer-reviewed, published, reliable, and valid research studies documenting the number or percentage of patients receiving gender affirming medical interventions who are helped by such procedures.

141. There are no long-term, peer-reviewed, published, reliable, and valid research studies documenting the number or percentage of patients receiving gender-affirming medical interventions who are injured or harmed by such procedures.

142. "Affirming" treatments have no known, peer-reviewed, and published error rates.

143. The gender-affirming approach has limited, very weak scientific support for short-term alleviation of dysphoria and no long-term outcomes data demonstrating superiority over the other approaches.

144. Because of the major methodological limitations and weaknesses of the extant published literature in the field of gender dysphoria, one cannot make a conclusion that "affirming" treatments are justified as a safe and effective long-term solution to gender dysphoria in consideration of the significant risks and unsubstantiated long-term benefits.

145. With the limited and poor-quality data currently available about the purported efficacy of blocking normally timed puberty, administering cross-sex hormones, and gender-affirming surgeries in alleviating psychological morbidity for youth who experience sex-discordant gender identity and the serious medical risks associated with these interventions, it cannot be concluded that this approach is "medically necessary." Use of such medical interventions remains a largely experimental approach.

146. Experimentation on gender-discordant youths is especially likely to cause harm to patients from historically marginalized communities. That is because children in such communities are disproportionally affected by gender discordance. These include:

- children with a history of psychiatric illness;[340]
- children of color;[341]
- children with mental developmental disabilities;[342]
- children on the autistic spectrum;[343] and
- children residing in foster care homes and adopted children.[344]

147. Patients suffering from gender dysphoria or related issues have a right to be protected from experimental, potentially harmful treatments lacking reliable, valid, peer-reviewed, published, long-term scientific evidence of safety and effectiveness.

148. The treatment protocols and recommendations of politically influenced, non-science associations like WPATH and the American Academy of Pediatrics that engage in consensus-seeking methodologies by vote rather than science are not based on competent, credible, methodologically sound science, and have no known or published error rate.

149. The committee that developed the Endocrine Society gender-dysphoria guidelines relied on low-quality scientific evidence in making strong treatment recommendations and failed to adequately review the scientific evidence pertaining to long-term risk of medical interventions to affirm sex-discordant gender identity

[340] See, e.g., R. Kaltiala-Heino et al., Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development, 9 Child Adolesc. Psychiatry Mental Health 9 (2015).
[341] See, e.g., G. N. Rider et al., Health and Care Utilization of Transgender and Gender Nonconforming Youth: A Population-Based Study, 141 Pediatrics e20171683 (2018).
[342] See, e.g., C. Bedard et al., Gender Identity and Sexual Orientation in People with Developmental Disabilities, 28 Sexuality and Disability 165 (2010).
[343] See, e.g., A. L. C. De Vries et al., Autism Spectrum Disorders in Gender Dysphoric Children and Adolescents, 40 J. Autism Dev. Disord. 930 (2010).
[344] See, e.g., D. E. Shumer et al., Overrepresentation of Adopted Adolescents at a Hospital-Based Gender Dysphoria Clinic, 2 Transgender Health 76 (2017).

150. Administering hormones to a child whose gender dysphoria is highly likely to resolve is risky, unscientific, and unethical. Iatrogenic damages from these interventions, including sterility, stunted growth, metabolic changes that increase risk of heart disease and diabetes, and many more, are often irreversible.

151. Because of these concerns about the safety, efficacy, and scientific validity of controversial, unproven, and experimental treatment paradigms, I have not personally engaged in the delivery of gender-affirming medical interventions to children with gender dysphoria. Given the unproven long-term benefits and the well-documented risks and harms of "transitioning" children, I decline to participate in such experimental treatments until the science has proven that the relative risks and benefits of this approach warrant such procedures.

152. My decision is strengthened by the knowledge that the vast majority of children who report gender dysphoria will, if not affirmed in their sex-discordant gender identity grow out of the problem — a natural coping-developmental process — and willingly accept their biological sex. Since there are no reliable assessment methods for identifying the small percentage of children with persisting sex-gender identity discordance from the vast majority who will accept their biological sex, and since puberty blocking treatments, hormone transition treatments, and surgical transition treatments are all known to have potentially life-long devastating, negative effects on patients, I and many colleagues view it as unethical to treat children with an unknown future by using experimental, aggressive, and intrusive gender affirming medical interventions.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on May 19, 2023.

Paul W Hruz

Paul W. Hruz, M.D., Ph.D.

Curriculum Vitae

Date: 3/19/2023
Name: Paul W. Hruz, M.D., Ph.D.

Contact Information

Office:	Phone: 314-286-2797 Fax: 314-286-2892
Mail:	Washington University in St. Louis School of Medicine Department of Pediatrics Endocrinology and Diabetes 660 South Euclid Avenue St Louis MO 63110
Email:	Office: hruz_p@wustl.edu

Present Position

Associate Professor of Pediatrics, Endocrinology and Diabetes
Associate Professor of Pediatrics, Cell Biology & Physiology

Education

1987	BS, Chemistry, Marquette University, Milwaukee, WI
1993	PhD, Biochemistry, Medical College of Wisconsin, Milwaukee, WI Elucidation of Structural, Mechanistic, and Regulatory Elements in 3-Hydroxy-3-Methlyglutaryl-Coenzyme A Lyase, Henry Miziorko
1994	MD, Medicine, Medical College of Wisconsin, Milwaukee, WI
1994 - 1997	Pediatric Residency, University of Washington, Seattle, Washington
1997 - 2000	Pediatric Endocrinology Fellowship, Washington University, Saint Louis, MO
2017	Certification in Healthcare Ethics, National Catholic Bioethics Center, Philadelphia, PA

Academic Positions / Employment

1996 - 1997	Locum Tenens Physician, Group Health of Puget Sound Eastside Hospital, Group Health of Puget Sound Eastside Hospital, Seattle , WA
2000 - 2003	Instructor in Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2003 - 2011	Assistant Professor of Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2004 - 2011	Assistant Professor of Pediatrics, Cell Biology & Physiology, Washington University in St. Louis, St. Louis, MO
2011 - Pres	Associate Professor of Pediatrics, Cell Biology & Physiology, Washington University in St. Louis, St. Louis, MO

2011 - Pres	Associate Professor of Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2012 - 2017	Division Chief, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO

Clinical Title and Responsibilities

	General Pediatrician, General Pediatric Ward Attending: 2-4 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Endocrinology Night Telephone Consult Service: Average of 2-6 weeks/per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 3-6 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Outpatient Endocrinology Clinic: Approximately 150 patient visits per month, St. Louis Children's Hospital

Teaching Title and Responsibilities

2009 - Pres	Lecturer, Markey Course-Diabetes Module
2008 – 2016	Fellowship Program Director- Pediatric Endocrinology and Diabetes
2020 - 2020	Facilitator, Reading Elective-Interdisciplinary/Miscellaneous Course #M80-800, Washington University School of Medicine
2019 – Pres	Associate Fellowship Program Director- Pediatric Endocrinology and Diabetes

University, School of Medicine and Hospital Appointments and Committees

University

2012 - 2020	Disorders of Sexual Development Multidisciplinary Care Program

School of Medicine

2013 - 2020	Molecular Cell Biology Graduate Student Admissions Committee
2014 - Pres	Research Consultant, ICTS Research Forum - Child Health

Hospital

2000 - Pres	Attending Physician, St. Louis Children's Hospital

Medical Licensure and Certifications

1997 - Pres	Board Certified in General Pediatrics
2000 - Pres	MO Stae License #2000155004
2001 - Pres	Board Certified in Pediatric Endocrinology & Metabolism

Honors and Awards

1987	National Institute of Chemists Research and Recognition Award
1987	Phi Beta Kappa
1987	Phi Lambda Upsilon (Honorary Chemical Society)
1988	American Heart Association Predoctoral Fellowship Award

1994	Alpha Omega Alpha
1994	Armond J. Quick Award for Excellence in Biochemistry
1994	NIDDK/Diabetes Branch Most Outstanding Resident
1998	Pfizer Postdoctoral Fellowship Award
2002	Scholar, Child Health Research Center of Excellence in Developmental Biology at Washington University
2013	Julio V Santiago, M.D. Scholar in Pediatrics
2017	Redemptor Hominis Award for Outstanding Contributions to the Study of Bioethics
2018	Eli Lilly Outstanding Contribution to Drug Discovery: Emerging Biology Award
2018	Scholar-Innovator Award, Harrington Discovery Institute
2021	Linacre Award

Editorial Responsibilities

Editorial Ad Hoc Reviews

	AIDS
	AIDS Research and Human Retroviruses
	American Journal of Pathology
	American Journal of Physiology
	British Journal of Pharmacology
	Circulation Research
	Clinical Pharmacology & Therapeutics
	Comparative Biochemistry and Physiology
	Diabetes
	Experimental Biology and Medicine
	Future Virology
	Journal of Antimicrobial Chemotherapy
	Journal of Clinical Endocrinology & Metabolism
	Journal of Molecular and Cellular Cardiology
	Obesity Research
2000 - Pres	Journal of Biological Chemistry
2013 - Pres	PlosOne
2016 - Pres	Scientific Reports
2018 - Pres	Nutrients

Editorial Boards

2014 - 2015	Endocrinology and Metabolism Clinics of North America

National Panels, Committees

2017 - Pres	Consultant, Catholic Health Association
2021 - Pres	Consulting Fellow, National Catholic Bioethics Center

National Boards

2020 - Pres	WU ICTS Clinical and Translational Research Funding Program (CTRFP) Review Committee

Professional Societies and Organizations

American Diabetes Association

Endocrine Society

Pediatric Endocrine Society

Major Invited Professorships and Lectures

2002	Pediatric Grand Rounds, St. Louis Children's Hospital, St Louis, MO
2004	National Disease Research Interchange, Human Islet Cell Research Conference, Philadelphia, PA
2004	NIDA-NIH Sponsored National Meeting on Hormones, Drug Abuse and Infections, Bethesda, MD
2005	Endocrine Grand Rounds, University of Indiana, Indianapolis, IN
2005	The Collaborative Institute of Virology, Complications Committee Meeting, Boston, MA
2006	Metabolic Syndrome Advisory Board Meeting, Bristol-Meyers Squibb, Pennington, NJ
2007	American Heart Association and American Academy of HIV Medicine State of the Science Conference: Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living with HIV/AIDS, Chicago, IL
2007	Minority Access to Research Careers Seminar, University of Arizona, Tucson, AZ
2007	MSTP Annual Visiting Alumnus Lecture, Medical College of Wisconsin , Milwaukee, WI
2007	Pediatric Grand Rounds, St Louis Children’s Hospital, St Louis, MO
2008	Division of Endocrinology, Diabetes and Nutrition Grand Rounds, Boston University, Boston, MA
2009	Pediatric Grand Rounds, St Louis Children's Hospital, St. Louis, MO
2010	American Diabetes Association Scientific Sessions, Symposium Lecture Orlando, FL
2010	School of Biological Sciences Conference Series, University of Missouri Kansas City, Kansas City, MO
2011	Life Cycle Management Advisory Board Meeting, Bristol-Myers Squibb,, Chicago, IL
2013	Pediatric Grand Rounds, St Louis Children's Hospital, ST LOUIS, MO
2013	Clinical Practice Update Lecture, St Louis Children's Hospital, St Louis, MO
2014	Pediatric Academic Societies Meeting,, Vancouver, Canada
2014	American Diabetes Association 74th Scientific Sessions, , San Francisco, CA
2017	Division of Pediatric Endocrinology Metabolism Rounds, University of Michigan, Ann Arbor, MI
2017	Catholic Medical Association National Conference, Denver, CO
2018	Obstetrics, Gynecology & Women's Health Grand Rounds, Saint Louis University, St. Louis, MO
2018	Medical Grand Rounds, Sindicato Médico del Uruguay, Montevideo, Uraquay
2018	Internal Medicine Grand Rounds, Texas Tech , Lubbock, TX
2019	Veritas Center for Ethics in Public Life Conference, Franciscan University, Steubenville, OH
2019	MaterCare International Conference, Rome, Italy
2019	Child Health Policy Forum, Notre Dame University, South Bend , IN

2021	Obstetrics & Gynecology Grand Rounds, University of Tennessee, Knoxville , TN
2022	The World Federation of Catholic Medical Associations (*FIAMC*), Rome, Italy

Consulting Relationships and Board Memberships

1996 - 2012	Consultant, Bristol Myers Squibb
1997 - 2012	Consultant, Gilead Sciences

Research Support

Completed Governmental Support

2001 - 2006	K-08 A149747, NIH Mechanism of GLUT4 Inhibition by HIV Protease Inhibitors Role: Principal Investigator
2007 - 2012	R01 Mechanisms for Altered Glucose Homeostasis During HAART Role: Principal Investigator Total cost: $800,000.00
2009 - 2011	R01 Student Supp Mechanisms for Altered Glucose Homeostasis During HAART Role: Principal Investigator Total cost: $25,128.00
2009 - 2014	R01 Direct Effects of Antiretroviral Therapy on Cardiac Energy Homeostasis Role: Principal Investigator Total cost: $1,250,000.00
2017 - 2019	R-21 1R21AI130584 , National Institutes of Health SELECTIVE INHIBITION OF THE P. FALCIPARUM GLUCOSE TRANSPORTER PFHT Role: Principal Investigator Total cost: $228,750.00

Completed Non-Governmental Support

2015	Novel HIV Protease Inhibitors and GLUT4 Role: Principal Investigator
2008 - 2011	II Insulin Resistance and Myocardial Glucose Metabolism in Pediatric Heart Failure Role: Co-Investigator PI: Hruz Total cost: $249,999.00
2009 - 2012	Research Program Regulation of GLUT4 Intrinsic Activity Role: Principal Investigator Total cost: $268,262.00
2010 - 2011	Protective Effect of Saxagliptin on a Progressive Deterioration of Cardiovascular Function Role: Principal Investigator
2012 - 2015	II Solution-State NMR Structure and Dynamics of Facilitative Glucose Transport Proteins Role: Principal Investigator Total cost: $375,000.00

2017 - 2020 Prevention And Treatment Of Hepatic Steatosis Through Selective Targeting Of GLUT8
Role: Co-Principal Investigator
PI: DeBosch
Total cost: $450,000.00

2017 - 2021 Matching Micro Grant
Novel Treatment of Fatty Liver Disease (CDD/LEAP)
Role: Principal Investigator
Total cost: $68,500.00

2018 - 2021 LEAP Innovator Challenge
Novel Treatment of Fatty Liver Disease
Role: Principal Investigator
Total cost: $68,500.00

2019 - 2021 Scholar-Innovator Award HDI2019-SI-4555 , Harrington Foundation
Novel Treatment of Non-Alcoholic Fatty Liver Disease
Role: Principal Investigator
Total cost: $379,000.00

Current Governmental Support

2021 - 2025 R-01 DK126622 (Co-investigator), 8/25/2021-7/31/2025, NIH-NIDDK, , NIH
Leveraging glucose transport and the adaptive fasting response to modulate hepatic metabolism
Role: Co-Investigator
PI: DeBosch

Trainee/Mentee/Sponsorship Record

2002 - 2002 Nishant Raj- Undergraduate Student, Other
Study area: Researcher

2002 - 2010 Joseph Koster, PhD, Postdoctoral Fellow
Study area: Researcher

2003 - 2004 Johann Hertel, Medical Student
Study area: Research
Present position: Assistant Professor, University of North Carolina, Chapel Hill, NC

2003 - 2003 John Paul Shen, Medical Student
Study area: Research

2004 - 2005 Carl Cassel- High School Student, Other
Study area: Research

2004 - 2004 Christopher Hawkins- Undergraduate Student, Other
Study area: Researcher

2004 - 2004 Kaiming Wu- High School Student, Other
Study area: Research

2005 - 2005 Helena Johnson, Graduate Student

2005 - 2005 Jeremy Etzkorn, Medical Student
Study area: Researcher

2005 - 2005 Dominic Doran, DSc, Postdoctoral Fellow
Study area: HIV Protease Inhibitor Effects on Exercize Tolerance

2006 - 2006 Ramon Jin, Graduate Student
Study area: Research

2006 - 2006 Taekyung Kim, Graduate Student
Study area: Research

2007 - 2007 Jan Freiss- Undergraduate Student, Other
Study area: Researcher

2007 - 2008 Kai-Chien Yang, Graduate Student
Study area: Research
Present position: Postdoctoral Research Associate, University of Chicago

2007 - 2007 Paul Buske, Graduate Student
Study area: Research

2007 - 2007 Randy Colvin, Medical Student
Study area: Researcher

2008 - 2011 Arpita Vyas, MD, Clinical Fellow
Study area: Research
Present position: Assistant Professor, Michigan State University, Lansing MI

2008 - 2009 Candace Reno, Graduate Student
Study area: Research
Present position: Research Associate, University of Utah

2008 - 2012 Dennis Woo- Undergraduate Student, Other
Study area: Researcher
Present position: MSTP Student, USC, Los Angeles CA

2008 - 2008 Temitope Aiyejorun, Graduate Student
Study area: Research

2009 - 2009 Anne-Sophie Stolle- Undergraduate Student, Other
Study area: Research

2009 - 2009 Matthew Hruz- High School Student, Other
Study area: Research
Present position: Computer Programmer, Consumer Affairs, Tulsa OK

2009 - 2009 Stephanie Scherer, Graduate Student
Study area: Research

2010 - 2014 Lauren Flessner, PhD, Postdoctoral Fellow
Present position: Instructor, Syracuse University

2010 - 2010 Constance Haufe- Undergraduate Student, Other
Study area: Researcher

2010 - 2011 Corinna Wilde- Undergraduate Student, Other
Study area: Researcher

2010 - 2010 Samuel Lite- High School Student, Other
Study area: Research

2011 - 2016 Thomas Kraft, Graduate Student
Study area: Glucose transporter structure/function
Present position: Postdoctoral Fellow, Roche, Penzberg, Germany

2011 - 2011 Amanda Koenig- High School Student, Other
Study area: Research

2011 - 2012 Lisa Becker- Undergraduate Student, Other

2011 - 2011 Melissa Al-Jaoude- High School Students, Other

2019 Ava Suda, Other, Pre-med

Bibliography

A. Journal Articles

1. Hruz PW, Narasimhan C, Miziorko HM. 3-Hydroxy-3-methylglutaryl coenzyme A lyase: affinity labeling of the Pseudomonas mevalonii enzyme and assignment of cysteine-237 to the active site. *Biochemistry*. 1992;31(29):6842-7. PMID:1637819
2. Hruz PW, Miziorko HM. Avian 3-hydroxy-3-methylglutaryl-CoA lyase: sensitivity of enzyme activity to thiol/disulfide exchange and identification of proximal reactive cysteines. *Protein Sci*. 1992;1(9):1144-53. doi:10.1002/pro.5560010908 PMCID:PMC2142181 PMID:1304393
3. Mitchell GA, Robert MF, Hruz PW, Wang S, Fontaine G, Behnke CE, Mende-Mueller LM, Schappert K, Lee C, Gibson KM, Miziorko HM. 3-Hydroxy-3-methylglutaryl coenzyme A lyase (HL). Cloning of human and chicken liver HL cDNAs and characterization of a mutation causing human HL deficiency. *J Biol Chem*. 1993;268(6):4376-81. PMID:8440722
4. Hruz PW, Anderson VE, Miziorko HM. 3-Hydroxy-3-methylglutaryldithio-CoA: utility of an alternative substrate in elucidation of a role for HMG-CoA lyase's cation activator. *Biochim Biophys Acta*. 1993;1162(1-2):149-54. PMID:8095409
5. Roberts JR, Narasimhan C, Hruz PW, Mitchell GA, Miziorko HM. 3-Hydroxy-3-methylglutaryl-CoA lyase: expression and isolation of the recombinant human enzyme and investigation of a mechanism for regulation of enzyme activity. *J Biol Chem*. 1994;269(27):17841-6. PMID:8027038
6. Hruz PW, Mueckler MM. Cysteine-scanning mutagenesis of transmembrane segment 7 of the GLUT1 glucose transporter. *J Biol Chem*. 1999;274(51):36176-80. PMID:10593902
7. Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem*. 2000;275(27):20251-4. doi:10.1074/jbc.C000228200 PMID:10806189
8. Hruz PW, Mueckler MM. Cysteine-scanning mutagenesis of transmembrane segment 11 of the GLUT1 facilitative glucose transporter. *Biochemistry*. 2000;39(31):9367-72. PMID:10924131
9. Hruz PW, Mueckler MM. Structural analysis of the GLUT1 facilitative glucose transporter (review). *Mol Membr Biol*. 2001;18(3):183-93. PMID:11681785
10. Murata H, Hruz PW, Mueckler M. Investigating the cellular targets of HIV protease inhibitors: implications for metabolic disorders and improvements in drug therapy. *Curr Drug Targets Infect Disord*. 2002;2(1):1-8. PMID:12462148
11. Hruz PW, Murata H, Qiu H, Mueckler M. Indinavir induces acute and reversible peripheral insulin resistance in rats. *Diabetes*. 2002;51(4):937-42. PMID:11916910
12. Murata H, Hruz PW, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. *AIDS*. 2002;16(6):859-63. PMID:11919487
13. Koster JC, Remedi MS, Qiu H, Nichols CG, Hruz PW. HIV protease inhibitors acutely impair glucose-stimulated insulin release. *Diabetes*. 2003;52(7):1695-700. PMCID:PMC1403824 PMID:12829635
14. Liao Y, Shikapwashya ON, Shteyer E, Dieckgraefe BK, Hruz PW, Rudnick DA. Delayed hepatocellular mitotic progression and impaired liver regeneration in early growth response-1-deficient mice. *J Biol Chem*. 2004;279(41):43107-16. doi:10.1074/jbc.M407969200 PMID:15265859
15. Shteyer E, Liao Y, Muglia LJ, Hruz PW, Rudnick DA. Disruption of hepatic adipogenesis is associated with impaired liver regeneration in mice. *Hepatology*. 2004;40(6):1322-32. doi:10.1002/hep.20462 PMID:15565660
16. Hertel J, Struthers H, Horj CB, Hruz PW. A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. *J Biol Chem*. 2004;279(53):55147-52. doi:10.1074/jbc.M410826200 PMCID:PMC1403823 PMID:15496402

17. Yan Q, Hruz PW. Direct comparison of the acute in vivo effects of HIV protease inhibitors on peripheral glucose disposal. *J Acquir Immune Defic Syndr*. 2005;40(4):398-403. PMCID:PMC1360159 PMID:16280693
18. Hruz PW. Molecular Mechanisms for Altered Glucose Homeostasis in HIV Infection. *Am J Infect Dis*. 2006;2(3):187-192. PMCID:PMC1716153 PMID:17186064
19. Turmelle YP, Shikapwashya O, Tu S, Hruz PW, Yan Q, Rudnick DA. Rosiglitazone inhibits mouse liver regeneration. *FASEB J*. 2006;20(14):2609-11. doi:10.1096/fj.06-6511fje PMID:17077279
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23. Tu P, Bhasin S, Hruz PW, Herbst KL, Castellani LW, Hua N, Hamilton JA, Guo W. Genetic disruption of myostatin reduces the development of proatherogenic dyslipidemia and atherogenic lesions in Ldlr null mice. *Diabetes*. 2009;58(8):1739-48. doi:10.2337/db09-0349 PMCID:PMC2712781 PMID:19509018
24. Guo W, Wong S, Pudney J, Jasuja R, Hua N, Jiang L, Miller A, Hruz PW, Hamilton JA, Bhasin S. Acipimox, an inhibitor of lipolysis, attenuates atherogenesis in LDLR-null mice treated with HIV protease inhibitor ritonavir. *Arterioscler Thromb Vasc Biol*. 2009;29(12):2028-32. doi:10.1161/ATVBAHA.109.191304 PMCID:PMC2783673 PMID:19762785
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26. Gazit V, Weymann A, Hartman E, Finck BN, Hruz PW, Tzekov A, Rudnick DA. Liver regeneration is impaired in lipodystrophic fatty liver dystrophy mice. *Hepatology*. 2010;52(6):2109-17. doi:10.1002/hep.23920 PMCID:PMC2991544 PMID:20967828
27. Hresko RC, Hruz PW. HIV protease inhibitors act as competitive inhibitors of the cytoplasmic glucose binding site of GLUTs with differing affinities for GLUT1 and GLUT4. *PLoS One*. 2011;6(9):e25237. doi:10.1371/journal.pone.0025237 PMCID:PMC3179492 PMID:21966466
28. Vyas AK, Yang KC, Woo D, Tzekov A, Kovacs A, Jay PY, Hruz PW. Exenatide improves glucose homeostasis and prolongs survival in a murine model of dilated cardiomyopathy. *PLoS One*. 2011;6(2):e17178. doi:10.1371/journal.pone.0017178 PMCID:PMC3040766 PMID:21359201
29. Hruz PW, Yan Q, Tsai L, Koster J, Xu L, Cihlar T, Callebaut C. GS-8374, a novel HIV protease inhibitor, does not alter glucose homeostasis in cultured adipocytes or in a healthy-rodent model system. *Antimicrob Agents Chemother*. 2011;55(4):1377-82. doi:10.1128/AAC.01184-10 PMCID:PMC3067185 PMID:21245443
30. Remedi MS, Agapova SE, Vyas AK, Hruz PW, Nichols CG. Acute sulfonylurea therapy at disease onset can cause permanent remission of KATP-induced diabetes. *Diabetes*. 2011;60(10):2515-22. doi:10.2337/db11-0538 PMCID:PMC3178299 PMID:21813803
31. Aerni-Flessner L, Abi-Jaoude M, Koenig A, Payne M, Hruz PW. GLUT4, GLUT1, and GLUT8 are the dominant GLUT transcripts expressed in the murine left ventricle. *Cardiovasc Diabetol*. 2012;11:63. doi:10.1186/1475-2840-11-63 PMCID:PMC3416696 PMID:22681646

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52. Tayebi N, Leon-Ricardo B, McCall K, Mehinovic E, Engelstad K, Huynh V, Turner TN, Weisenberg J, Thio LL, Hruz P, Williams RSB, De Vivo DC, Petit V, Haller G, Gurnett CA. Quantitative determination of SLC2A1 variant functional effects in GLUT1 deficiency syndrome. Ann Clin Transl Neurol. 2023 May;10(5):787-801. doi: 10.1002/acn3.51767. Epub 2023 Mar 31. PMID: 37000947; PMCID: PMC10187726.

C2. Chapters

1. Henderson KE, Baranski TJ, Bickel PE, Clutter PE, Clutter WE, McGill JB. Endocrine Disorders in HIV/AIDS. In: *The Washington Manual Endocrinology Subspecialty Consult* Philadelphia, PA; 2008:321-328.
2. Paul W Hruz. Medical Approaches to Alleviating Gender Dysphoria In: Edward J Furton, eds. *Transgender Issues in Catholic Health Care* Philadelphia PA; 2021:1-42.
3. Cara Buskmiller and Paul Hruz. A Biological Understanding of Man and Woman In: John Finley, eds. *Sexual Identity: The Harmony of Philosophy, Science, and Revelation* Steubenville OH; 2022:Chapter 2, pp 65-103.

C4. Invited Publications

1. Grunfeld C, Kotler DP, Arnett DK, Falutz JM, Haffner SM, Hruz P, Masur H, Meigs JB, Mulligan K, Reiss P, Samaras K, Working Group 1. Contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors. *Circulation*. 2008;118(2):e20-8. PMCID: PMC3170411 PMID: 18566314
2. Hruz PW. HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*. 2008;3(6):660-5. PMCID: PMC2680222 PMID: 19373039

3. Hruz PW. Molecular mechanisms for insulin resistance in treated HIV-infection. *Best Pract Res Clin Endocrinol Metab*. 2011;25(3):459-68. PMCID: PMC3115529 PMID: 21663839
4. Hruz PW. HIV and endocrine disorders. *Endocrinol Metab Clin North Am*. 2014;43(3): xvii–xviii. PMID: 25169571
5. Hruz PW. Commentary. *Clin Chem*. 2015;61(12):1444. PMID: 26614228
6. Hruz PW, Mayer LS, and McHugh PR. Growing Pains: Problems with Pubertal Suppression in Treating Gender Dysphoria *The New Atlantis*. 2017;52:3-36.
7. Hruz, PW. The Use of Cross-Sex Steroids in Treating Gender Dysphoria *Natl Cathol Bioeth Q*. 2018;17(4):1-11.
8. Hruz, PW. Experimental Approaches to Alleviating Gender Dysphoria in Children *Nat Cathol Bioeth Q*. 2019;19(1):89-104.

Expert Witness Testimony

2009 Rosas v. Astrazeneca

2012 O'Connor v. Stamford

2016 Carcaño et al. v. Patrick McCrory (United States District Court, M.D. North Carolina)

2016 Jane Doe v. Board of Education of the Highland School District (United States District Court For the Southern District of Ohio Eastern Division, Case No. 2:16-CV-, 524)

2017 Ward v. Janssen (Circuit Court of St Louis, Division 16, MO, Case No. 1522-CC00213-01)

2017 Adams v. St John's School Board (United States District Court For the Middle District of Florida, FL Civil Action No. 3:17-cv-00739-TJCJBT)

2017 Ashton Whitaker v. Kenosha Unified School District (United States District Court Eastern District of Wisconsin, Civ. Action No. 2:16-cv-00943)

2018 Terri Bruce v. State of South Dakota (The United States District Court District of South Dakota Western Division, Case No. 17-5080)

2019 Cause DF-15-09887-SD of the 255th Judicial Circuit of Dallas County, TX regarding the dispute between J.A. D.Y. and J.U. D.Y., Children

2021 Kadel vs. Falwell (The United States District Court For The Middle District Of North Carolina, Case No.: 1:19-cv-272-LCB-LPA)

2022 Brandt v Rutledge (The United States District Court Eastern District of Arkansas Central Division, Case No. 4:21-CV-00450-JM)

2022 Eknes-Tucker vs Ivey (United States District Court Middle District of Alabama Northern Division, Case 2:22-cv-00184-LCB-SRW)

2022 D.H. et al. v. Snyder (United States District Court For the District Court of Arizona, Case No. 4:20-cv-00335-SHR)